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A.M.A. ARCHIVES OF OPHTHALMOLOGY

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Studies on Intraocular Effects of the Orbital Parasympathetic Pathway
Mansour F. Armaly

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Clinical Notes
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Lids, Lacrimal Apparatus, and Conjunctiva
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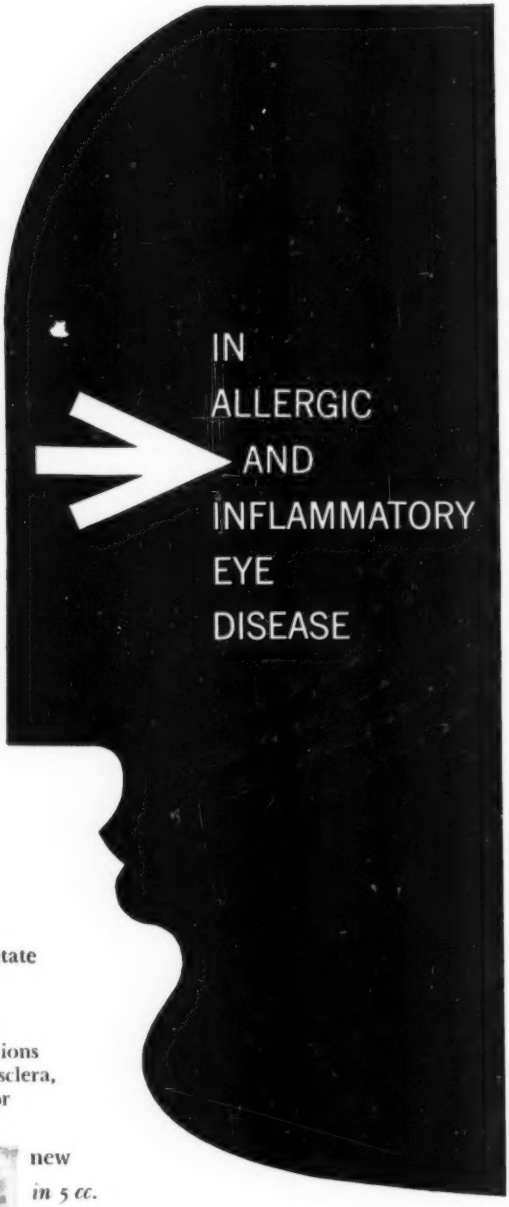

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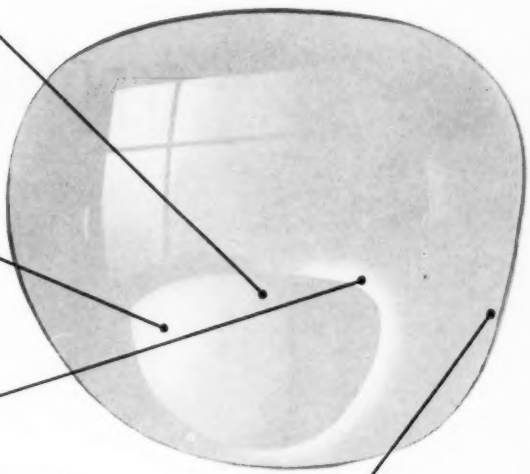

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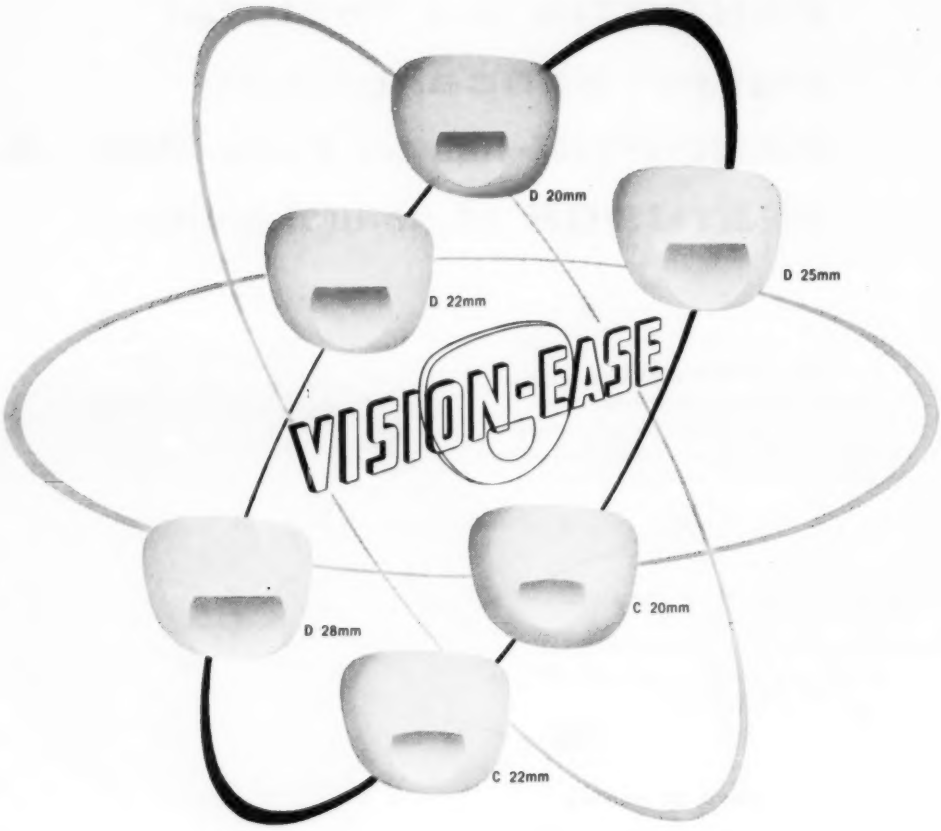

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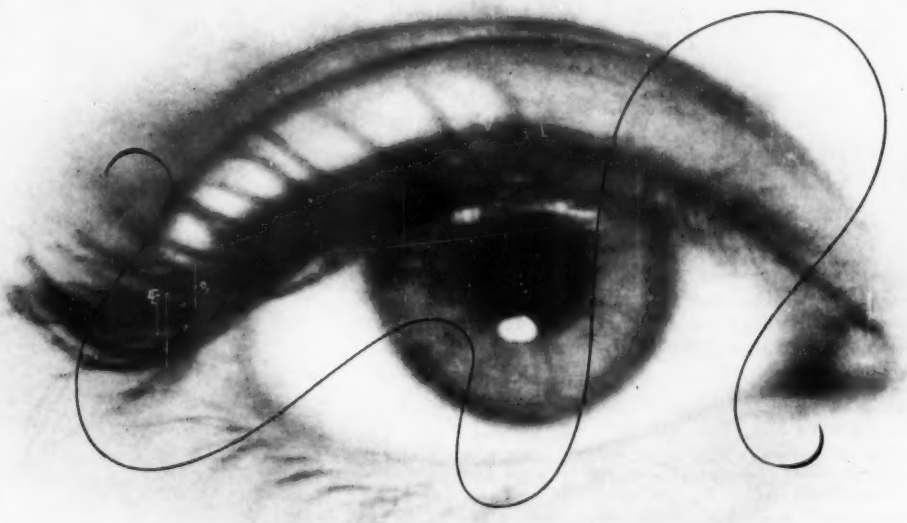

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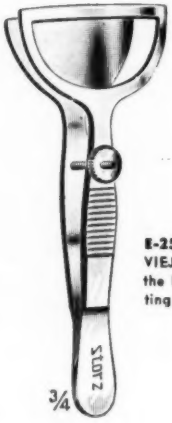

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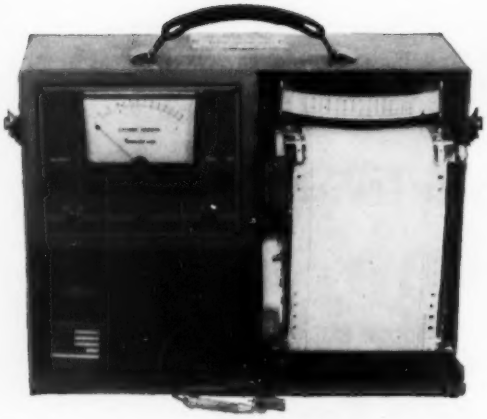

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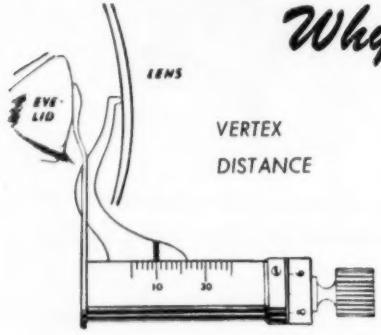

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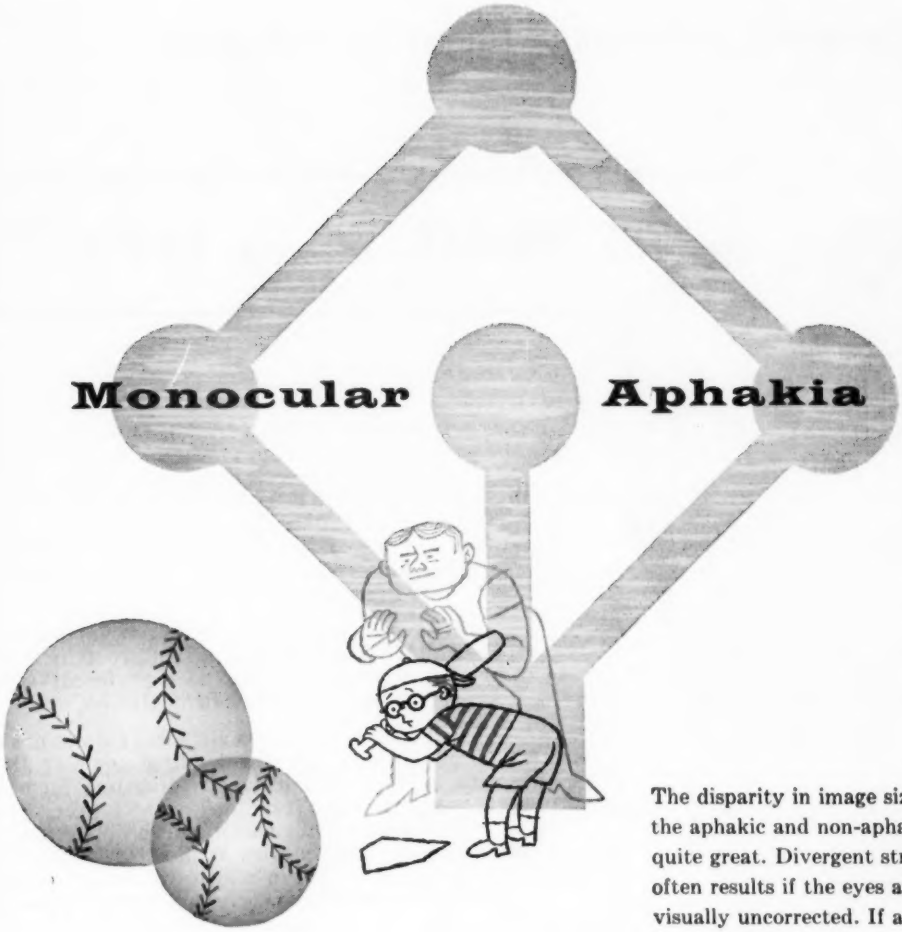

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An interesting case occurred a few days ago which illustrates how two small errors can cause a lot of trouble.

We made two pairs of glasses for a railroad executive who does a great deal of close work. His prescription reads as follows—right: + 2.00 + 1.00 × 180; left: + 2.50 + 1.00 × 180.

He returned after getting his new prescription filled and complained that while one pair of glasses was very comfortable, the other pair could be worn for only a short time, after which they were most uncomfortable.

We checked horizontal and vertical centers, power and axis on both pairs. The power of the lenses and the axis of the cylinders were in strict accord with the prescription and identical. We found, however, that the distance center of the left lens in the pair causing trouble was one millimeter higher than the distance center of the right lens, whereas the distance centers in the comfortable pair were exactly the same height.

A difference of one millimeter in centers in a lens strength of + 2.00 + 1.00 × 180 would produce .3 degree of prism, base up, in that eye—enough to cause some trouble for a very sensitive pair of eyes. On closer examination of the prescription, we found that the left eye having a half diopter more power in the vertical meridian than the right eye would exercise a vertical imbalance at a reading point eight millimeters down from the distance center of .4 degree of prism, base up, in that eye. This imbalance, added to the .3 degree of prism caused by the distance center being one millimeter higher made a .7 degree of prism, base up, in the left eye, which was enough to cause the trouble.

The left lens was reground, the distance center moved downward one millimeter and the patient is now comfortable with either pair of glasses.

To some this small error in centering may seem insignificant, but in this particular case it represented the difference between a satisfied patient and a dissatisfied one.

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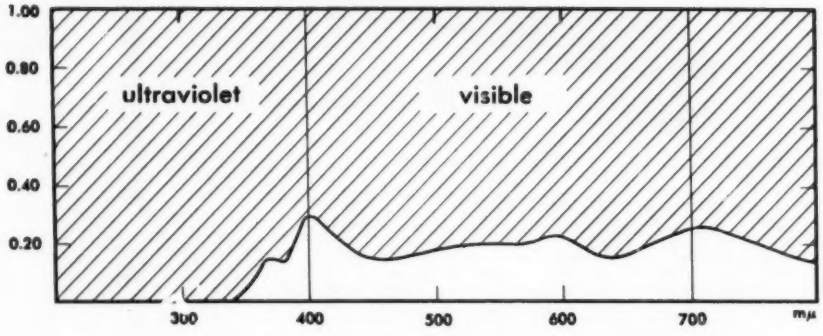

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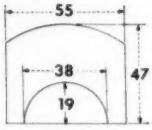

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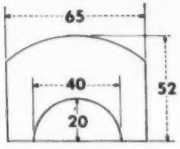

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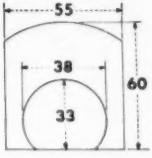

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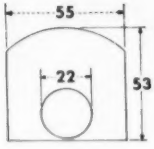

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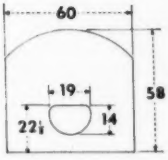

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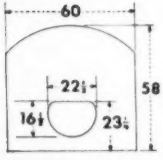

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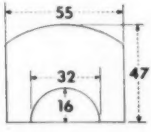

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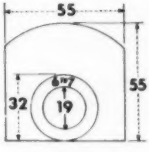

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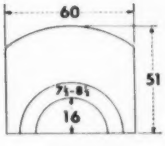

ULTEX X
50% Intermediate

ULTEX CATARACT
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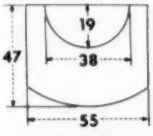

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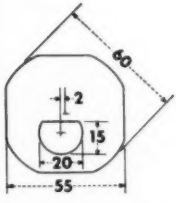

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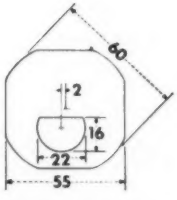

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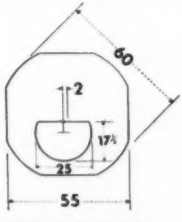

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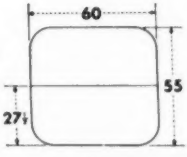

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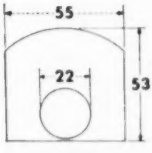

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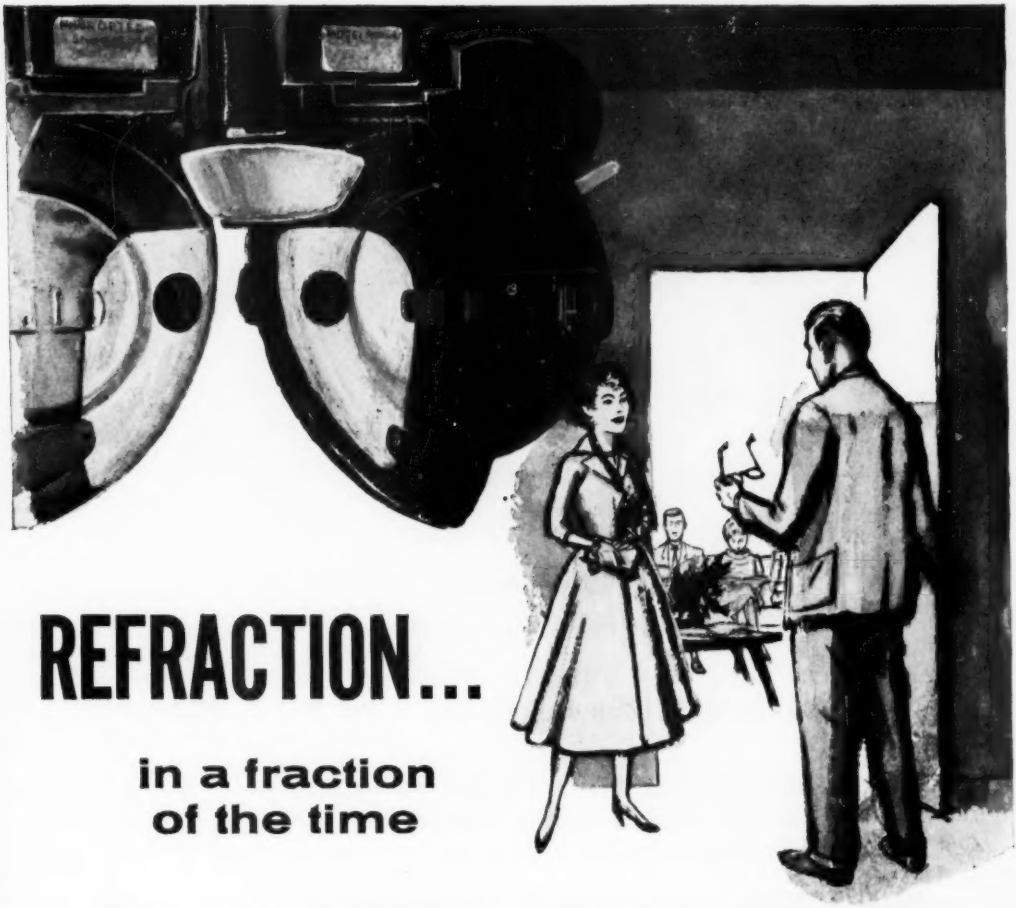

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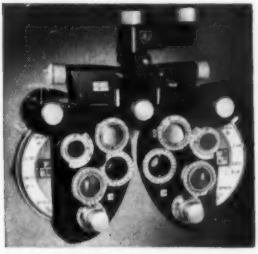

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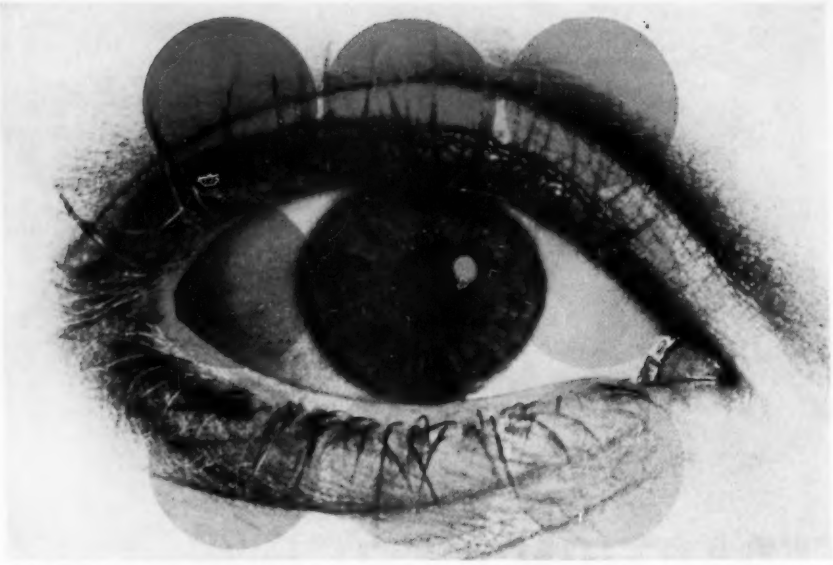

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1. New and Nonofficial Drugs; J. B. Lippincott Company, Philadelphia, 1958, p. 243.

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How Important Are Peripheral Fields?

FRED G. BLUM Jr., M.D.; L. KEITH GATES, M.D., and BURTON R. JAMES, M.D., Ann Arbor, Mich.

Introduction

In the Department of Ophthalmology at the University of Michigan it was noted that the peripheral fields rarely demonstrated a defect that the central fields (Bjerrum screen) failed to show. It was this observation that initiated the present study. In this paper it is not our intention to discuss the ultimate fine points that might be gleaned with research field techniques but rather to emphasize that our methods closely approximate the techniques used in the average clinic and ophthalmologist's office.

J. P. F. Lloyd summed up the situation well by stating, ". . . there is no provision for anything between the magnificent fields taken by Traquair and his literal followers which appear in publications such as that of Hughes (1943) on the one hand, and on the other the hurried scrawlings and weird frescoes found attached to hospital notes, such as these. . . . It is important to realize that only in ideal and comparatively rare circumstances is it possible for a field to be charted with real scientific accuracy." [1]

Review of Literature

The available literature (printed in the English language) for the past 40 years was reviewed and analyzed for comparisons of peripheral versus central fields. No such comparisons could be found, although several allusions to the problem were discovered.

Submitted for publication June 13, 1958.

A. J. McLean reminds us, ". . . Bjerrum, fifty years ago, used merely the back of his consultation room door." [2] He goes on to say, "The accuracy and utility of a tangent screen diminishes rapidly beyond 35° to 38° from the fixation point, so that it is not customary to have the screen more than 70° to 80° wide, but inasmuch as probably 95% of all significant ophthalmo-neurological lesions are quantitively discoverable readily within this area, supplemental use of the fussy and exhausting 180° perimeter is a rare necessity." [2]

Selection of Cases

Originally we selected all the consecutive fields that were performed in the clinic service for the calendar years of 1954, 1955, and part of 1956. As we were concerned primarily with the comparison of central and peripheral fields, the term "paired fields" was applied to central and peripheral fields performed on the same date.

Consecutive paired fields were performed on 1892 patients, some of whom had had paired fields recorded many years prior to the specific span of this study (in fact, some as far back as 1928). Thus, including all the paired fields on this group of patients, a total of 3078 paired fields was available for comparison. During the last 30 years, 72 residents in ophthalmology have completed their training in the department. These records provide, therefore, an excellent cross section of the work performed by this group of residents.

Field Techniques Used

The technique that has been considered more or less standard at the University Hospital is to use a 2 mm white test object at 330 mm. with either a standard Ferree Rand type or a Harrington "black light" perimeter. In routine perimetry testing, for the most part no attempt was made to test other than the outermost isopters. For the 1 meter tangent screen, made of unstitched black felt and illuminated with 7 ft-c. of light, a 2 mm. white test object at 1000 mm. is used. A 0.5 mm. white test object at 1000 mm. is used for central scotoma testing.

What Constitutes a Normal Field?

In trying to set up criteria for a normal central field, little difficulty was experienced, as the field was usually full out to the 25 degree borders, or it was definitely decreased in size, or it showed enlarged blind spots, a central scotoma, or other paracentral lesion. Having each spent considerable time testing fields, we had no difficulty in agreeing whether or not either a central or peripheral field was normal or abnormal. However, when an attempt was made to apply definite critera to the peripheral fields difficulty was immediately encountered.

When the values as quoted in the perimetry texts were reviewed, it was found that a 2 mm. white object at 330 mm. was supposed to be seen temporally to 85 degrees, nasally to 60 degrees, superiorly to 50 degrees, and inferiorly to 65 degrees.[3] When this "average" was applied to this series, the majority of the fields fell into an abnormal range, which seemed to be most unlikely. Zuckerman states, ". . . within certain limits, the shape rather than the size of the field is more important for diagnosis."[4] John N. Evans states, "Uniform contraction of the fields was of relatively little significance for interpretation. . . . The shape of the field was most significant."[5]

Traquair states, "Uniform depression suggests the probability of a functional as against an organic cause."[6]

Ferree, Rand, and Monroe have found the following to be true in their perimetry studies: "We find in general the largest average breadth of field for the emmetrope group. In order from the largest to smallest the groups rank as follows: emmetropes, hyperopes, myopes and presbyopes."[7] They also say, "The range of breadth of field for the 0.17 degree stimulus is 34.3 to 58.5 degrees; for the one-degree stimulus 60.3 to 73.1 degrees."[7] (Note: A 0.17 degree test object equals a 1 mm. test object at a 330 mm. test distance and a 1 degree test object equals a 6 mm. test object at a 330 mm. test distance.)

Supported by the experience of the foregoing authors, we decided to consider peripheral fields normal as long as the depression was uniform and equal in both eyes and essentially concentric with the outlines of the "normal" field. However, we arbitrarily considered as abnormal any field depressed to less than 65 degrees in the horizontal temporal meridian, even though fields of both eyes were completely symmetrical. Of course, if any difference of 10 degrees or over existed in any particular meridian between the two eyes, no matter how full the fields, these were considered abnormal. This somewhat arbitrary limit would certainly fit well within the limits of normal as set by Ferree, Rand, and Monroe when a 2 mm. test object is used at 330 mm. As fields are tested, at this hospital, the examiner records his impression of the normality or abnormality of the fields in view of the patient's attentiveness, mental alertness, experience, cooperation, etc. In borderline cases, it was occasionally necessary to rely on these notations made at the time of the actual examination.

With use of the preceding criteria, the following is the break-down of the 3078 examinations where both peripheral and central fields were examined.

There were 1244 examinations in which both the central and peripheral fields were positive. In 1403 examinations there were no defects in either the peripheral or the central field. In 406 examinations there

Distribution of Examinations by Number and by Etiological Classification

Diagnosis	Cases, No.	Central Negative & Peripheral Positive	Both Positive	Both Negative	Central Positive & Peripheral Negative
Psychiatric	136	1	36	98	18
Metabolic	79	1	32	59	8
Glaucoma	162	1	446	202	62
Glaucoma suspects	17	0	4	21	7
Headaches	133	2	13	127	14
Brain tumors (diagnosed)	74	0	115	48	50
Multiple sclerosis	61	2	22	59	15
Neurological diseases	285	11	248	132	56
Convulsive disorders	209	2	52	176	22
Misc. ocular & systemic diseases	736	5	276	481	154
Totals	1,892	25	1,244	1,403	406

were central defects not found on peripheral examination, and in 25 examinations there were peripheral defects not found on central examination. A more detailed break-down by number and by etiological classification is given in the Table.

As was stated in the introductory paragraph of this paper, the peripheral fields rarely provided information which the central fields failed to furnish. Because of this foregoing statement, it is particularly necessary to provide the reader with further details relative to the 25 sets of paired fields in which the peripheral fields were positive and the central fields, negative.

These 25 sets of paired fields represented field recordings on 22 different persons in a total series represented by 3078 paired fields and 1892 patients. Twenty-seven different diagnoses had been assigned to the 22 patients in this group; most of these diagnoses were firmly established, although six were only suspected (that is, suspected for more than three years but never confirmed), and one was an extremely questionable diagnosis of brain tumor.

Classification of these various diagnoses was attempted, but it proved to be impractical owing to the protean character of the conditions and the low incidence of each. Eleven of the twenty-two patients had more than one diagnosis which might have contributed to the respective field changes, but only seven diagnoses appeared more than once. The incidence of these seven conditions was as follows: lens opacities, two cases; multiple sclerosis, three cases (one firmly diagnosed, two suspected); brain-tumor suspects, two cases (one questionable, one extremely questionable); residual cerebrovascular accident, two cases (one firmly diagnosed, one questionable); headache, two cases; psychoneuroses, three cases, and convulsive disorders, four cases.

Each of the other diagnostic categories in this series was represented by only a single case. Owing to the varied nature of these 22 cases and the impossibility of placing them in a few major categories, a brief explanatory note pertinent to each has been included for the reader.

CASE 1.—Diagnosis: (1) retinal cysts, (2) peripheral cystic retinal degeneration, (3) retinal atrophy, and (4) corneal guttata.

Explanation: Upon ophthalmoscopic examination, this patient demonstrated large areas of cystic retinal degeneration which were consistent in size and location with the peripheral-field defects recorded. This condition was detected readily without peripheral-field testing.

CASE 2.—Diagnosis: (1) cancer of the right breast and (2) early senile cataracts.

Explanation: The recorded impression of the examining ophthalmologist was as follows: "Peripheral fields show generalized depression not characteristic of any specific disease. Central fields are within normal limits." The last note on this record (two years after the above fields) stated that the x-ray showed suspicious evidence of metastasis in the left lung but that there had been no change during the past two years. There was no mention of any intracranial metastasis. This patient had been treated in the neuropsychiatric institute and, except for the possibility that there may have been some functional component in this case, we can-

not adequately account for the peripheral-field depression exhibited.

CASE 3.—Diagnosis: (1) optic atrophy and (2) retrobulbar neuritis.

Explanation: These peripheral fields were symmetrical except for a slight nasal depression. No subsequent fields were recorded, and no central scotoma was detectable to 0.5 mm. white at 1000 mm. There was a definite temporal pallor of the discs, and the best corrected visual acuity was 20/50 O. D. and 20/60 O. S. Four years earlier central fields had shown a question of small central scotomas to 0.5 mm. white test object at 1000 mm. O. U. The impression of the ophthalmologist was that there was a partial optic atrophy probably due to old retrobulbar neuritis which was most likely the result of multiple sclerosis. However, neurological consultants on two occasions (Feb. 3, 1943, and July 22, 1952) did not feel there was sufficient supporting evidence for establishing the diagnosis of multiple sclerosis. Borderline EEG (July 30, 1952) was of no localizing value. We have no satisfactory explanation for the minor peripheral-field depression in this case.

CASE 4.—Diagnosis: (1) exophthalmos O. U., (2) anisocoria, (3) lagophthalmos O. D., (4) exposure keratitis, and (5) hypertensive retinopathy, grade III.

Explanation: A total of three paired fields was recorded in this case. The first central field was negative; the peripheral field showed suspicious changes characterized by slight depression of the left field in the superior temporal quandrant. Two subsequent sets of paired fields demonstrated both central and peripheral defects. The last set showed a depression in the upper nasal quandrant of the right central field; the right peripheral field was full in all meridians. The left central field was full, but the left peripheral field showed generalized depression, especially superiorly, nasally, and inferiorly. This patient received irradiation to the pituitary gland late in 1951. The abnormal visual fields were recorded two, three, and three and one-half years, respectively, after the irradiation therapy. It also seems of importance to note that the field changes were not constant in location or in density. Certainly, in this case, various factors related to the exophthalmos, lagopthalmos, exposure keratitis, and hypertensive retinopathy may have contributed to the variability of the field changes noted. When the patient was last seen, in 1955, there were no other diagnoses given which might better account for the visual field changes recorded in this case.

CASE 5.—Diagnosis: trigeminal ganglion block.

Explanation: Depression of the right nasal peripheral field was recorded on Oct. 27, 1954, and on Aug. 2, 1956. The right peripheral field was completely normal in contour, while the left peripheral field demonstrated temporal depression. The central fields were completely normal on each of these occasions. This patient gave an 11-year history of headaches involving the right side of the face. These headaches were finally relieved in August, 1956, by an alcohol block of the right Gasserian ganglion. All diagnostic studies, including skull films, electroencephalograms, and chemical tests had been of no appreciable help in establishing a definite diagnosis, and, since the abnormal peripheral fields were recorded prior to the alcohol injection, we have no straight-forward explanation for the recorded field changes in this case.

CASE 6.—Diagnosis: (1) convulsive disorder and (2) chronic brain syndrome.

Explanation: On two successive field examinations (three days apart) this patient's records revealed a defect in the upper temporal quandrant of the right field. This was accompanied by normal central fields. The examining ophthalmologist's note was as follows: "There is a defect in the peripheral field up and out which I cannot explain. The retina appears normal in this area." The electroencephalogram (Oct. 1, 1946) interpretation was as follows: "E. E. G. shows generalized abnormality of mild to moderate character compatible with a

grand mal type of convulsive disorder—no localization." EEG recorded on June 7, 1956, showed essentially the same characteristics as the one 10 years earlier. We have no satisfactory explanation for the peripheral-field defect which was recorded.

CASE 7.—Diagnosis: (1) convulsive disorder, (2) temporal lobe disorder, and (3) petit mal seizures.

Explanation: The examining ophthalmologist's impression on Dec. 15, 1954, was as follows: "Moderate temporal depression of peripheral fields, probably normal." No subsequent visual fields were recorded, and the last information relative to this patient's condition was dated April 20, 1955. This note stated, "Patient getting along well. Considering issuing driver's license." We have no adequate explanation for the peripheral-field depression recorded in this case.

CASE 8.—Diagnosis: (1) coronary lens opacities, (2) headaches, and (3) reactive depression.

Explanation: Postive peripheral and negative central fields were recorded on Aug. 13, 1954. Thirty-four months later, at the time of the last examination, there was still no evidence of an organic basis for the headaches but the coronary lens opacities were of a size and shape which could account for the peripheral-field defects.

CASE 9.—Diagnosis: (1) brain tumor suspect, (2) question of residual of old cerebrovascular accident, and (3) "diagnosis is not clear."

Explanation: The diagnosis in this case was never well defined. For a period of three years, a brain tumor or the residual of an old cerebrovascular accident had been entertained as the most likely diagnosis. Although the examining ophthalmologist's impression was that the peripheral and central fields were normal, this case was included in this series because the central fields were suggestive of a slight peripheral depression according to the criteria previously established for this study.

CASE 10.—Diagnosis: multiple sclerosis.

Explanation: This patient demonstrated temporal pallor of the optic discs, internuclear ophthalmoplegia, and multiple gaze palsies, as well as ataxia and slurred and dysarthric speech. Only one set of paired fields was recorded. This revealed a normal central field and a peripheral field with peripheral depression. This case had been firmly diagnosed as multiple sclerosis, and the patient was last examined two years after the generally depressed peripheral fields were recorded. The diagnosis remained the same, and there was no other explanation given to account for the recorded field changes.

CASE 11.—Diagnosis: (1) migraine headache and (2) psychoneurosis, conversion type.

Explanation: The examining ophthalmologist's impression of fields was recorded as follows: "Peripheral fields show generalized depression not diagnostic of any specific disease. Central fields normal at this time."

The concluding remark on the chart relative to the electroencephalogram findings was as follows: "A deep level trigger of some diffuse intracranial or metabolic condition could not be excluded, although the record was not that of a purely psychiatric condition nor was this the type of picture seen in migraine." There were no other explanations found for the peripheral-field defects.

CASE 12.—Diagnosis: meningoencephalitis.

Explanation: This case was diagnosed as meningoencephalitis of unknown etiology. There was depression of the left temporal and the right nasal peripheral fields recorded on Aug. 13, 1956; however, just 11 days later completely normal peripheral and central fields were found.

Possibly these findings were consistent with the more acute and the convalescent phases of the disease, respectively.

CASE 13.—Diagnosis: Meniere's disease.

Explanation: Meniere's disease was the suspected diagnosis in this case. A suggestion of early peripheral depression of the

fields was recorded on March 2, 1954, but just two days later both the peripheral and central fields were reported as entirely normal.

No definite final diagnosis was established in this case. The patient was not reexamined at this institution, and it is impossible to explain adequately the initial peripheral-field depression followed by normal peripheral and central fields two days later.

CASE 14.—Diagnosis: brain tumor suspect.

Explanation: This patient was examined on only one occasion at this institution. A positive diagnosis of brain tumor was never definitely established. The examining ophthalmologist reported depression of the peripheral field with a 2 mm. white at 330 mm. and a normal peripheral field with a 4 mm. white at 330 mm. The central fields were recorded as normal, although a 1 mm. white test object at 1000 mm. was used for central scotoma detection rather than our standard 0.5 mm. white test object at 1000 mm. No further follow-up was available in this case.

CASE 15.—Diagnosis: (1) question of myelitis and (2) question of multiple sclerosis.

Explanation: The examining ophthalmologist reported mild peripheral depression but nothing diagnostic. The patient was last examined 14 months after the suspicious fields were recorded, but no subsequent fields were recorded and no definite diagnosis was established.

We have no completely satisfactory explanation for the field findings in this case.

CASE 16.—Diagnosis: (1) subarachnoid hemorrhage and (2) aphakia.

Explanation: In this instance, the central field was tested with a 3 mm. white at 1000 mm. instead of the usual 2 mm. white at 1000 mm. One might conjecture that had the usual 2 mm. white test objects at 1000 mm. been employed in this case, some alteration in the central field might have been found. At any rate, this case probably should not be as seriously compared as the others, since the testing was not done according to our usual standards. Furthermore, the examiner's note was as follows: "Visual fields normal for aphakia."

Peripheral-field depression was considered to be the result of aphakia with possibly some influence by subarachnoid hemorrhage.

CASE 17.—Diagnosis: angle-closure glaucoma.

Explanation: This case raises an extremely interesting point. In all the records studied, this is the only glaucoma case which showed positive peripheral fields in conjunction with negative central fields. Furthermore, this was a patient who exhibited angle-closure glaucoma (which should have been detectable by other means of examination) and demonstrated three sets of normal paired fields during the 12 months after the recording of abnormal fields. The tonometer tension was 22.0 O. D. and 27.4 O. S. immediately before the single abnormal field examination.

Difficulty is encountered in adequately accounting for the early peripheral-field depression, because normal fields were repeatedly recorded at later dates when the tension level was even slightly higher.

CASE 18.—Diagnosis: pterygium O. S.

Explanation: On Nov. 29, 1954, the examining ophthalmologist reported a nasal peripheral-field defect due to a pterygium and on July 13, 1955, after a pterygium transplant, normal peripheral fields were recorded. The peripheral-field defect was considered to be due to the pterygium.

CASE 19.—Diagnosis: psychomotor epilepsy.

Explanation: In this instance, the peripheral fields, according to our criteria for this study, suggested slight peripheral depression; however, the examining ophthalmologist reported normal visual fields. An electroencephalogram three days later was interpreted as follows: "This type of focus is very highly suggestive of psychomotor or other temporal lobe seizure phenomena. A brain tumor is not suspected at this time."

The clinical findings in this case seemed to mesh well with the foregoing interpreta-

tions, and the final diagnosis of psychomotor epilepsy was assigned.

We have no satisfactory explanation for the suggestion of peripheral-field depression.

CASE 20.—Diagnosis: (1) multiple sclerosis, (2) paresis of right inferior oblique, and (3) small central corneal scar O. S.

Explanation: This case had been diagnosed as multiple sclerosis. The corneal scar did not appear large enough to cause a significant field defect, and certainly it was not situated in a position which would cause one to anticipate a major peripheral-field defect.

The examining ophthalmologist's note was as follows: "peripheral fields show depression of right lateral field; this could only be located in optic nerve."

The optic discs were normal, and the otological and neurosurgical consultants felt there was no evidence of a surgical lesion at the time of examination. There was no follow-up information available in this case; consequently, we have no further explanation for the field defects recorded.

CASE 21.—Diagnosis: (1) psychoneurosis and (2) convulsive disorder.

Explanation: The examining ophthalmologist's notation was as follows: "Question of temporal depression of minimal nature." No subsequent fields were tested, and no further hospitalizations were recorded at this institution.

The electroencephalogram interpretation was as follows: "Record is abnormal and paroxysmal, indicative of epilepsy. Temporal lobe seizure is likley. A focal, deep, non-neoplastic triggering lesion is possible. The record does not suggest a tumor."

CASE 22.—Diagnosis: (1) partial external ophthalmoplegia and (2) peripheral chorioretinitis.

Explanation: This patient had suffered a cerebral hemorrhage four months prior to field testing. Diplopia was noted on left lateral gaze, but this had been decreasing, although the patient still had a slight head tilt at the time of field testing. In addition, this patient demonstrated some areas of peripheral chorioretinitis; however, these areas were sufficiently small that they probably did not contribute significantly to field changes. The peripheral-field changes demonstrated a general depression bilaterally without any particular sector being affected primarily. We have no specific explanation for the fields as recorded in this case.

Comment and Conclusions

In this study an effort has been made to evaluate, as objectively as possible, a series of peripheral fields versus central fields performed in a large university ophthalmology service. The prime purpose has been to secure, if possible, an index to the real needs and specific indications for peripheral-field testing in the office of the average ophthalmologist.

While it is theoretically the best medical practice to do every test and examination, practically speaking, this is impossible. One must simply rely on one's past training and clinical experience to decide which tests may be helpful and which tests may be safely omitted.

It must be remembered that by and large the initial decision as to whether fields should or should not be tested is based almost entirely on clinical judgment, and once the decision to do fields is made, it should not necessarily be considered automatic that both peripheral and central fields be done every time; this too should be controlled by clinical evaluation. If this were not the case, fields would be routine for everyone seen in the clinic and office. An analogy that might be made is that most ophthalmologists rather arbitrarily set the age limit for taking tensions at an age above 35 or 40 and with a relatively clear conscience do not worry about those in the younger groups, yet it is known that glaucoma can and does occur in this younger group. It must be kept in mind that routine tests are clinically valuable only when they yield a maximum amount of information with a minimum amount of time spent; if one is to disagree with this concept, one would then be of the general opinion that every test known should be performed on everyone for fear of some-

time missing some additional bit of information.

In this series of 1892 consecutive patients on whom 3078 paired fields were performed, only 25 fields representing 22 patients showed positive peripheral and negative central fields. Of these, some represented conditions such as a pterygium and cortical lens opacities.

Two of the disease entities which interest the ophthalmologist and are of great concern to him are brain tumors and glaucoma. Establishment of the diagnosis of these entities is often aided by the visual-field examination. In this study, which included 74 patients with positively diagnosed brain tumor, not one case demonstrated positive peripheral and negative central fields. In the 162 positively diagnosed cases of glaucoma there was only 1 case in which a central field was negative and a peripheral field, positive. This was a case of previously diagnosed narrow-angle glaucoma which subsequently had three paired fields, all of which were completely negative.

There certainly exist conditions that we have seen and remembered, such as retinal detachments and cerebrovascular accidents, where small peripheral-field defects occurred. Neither of these conditions happened to appear in the 1892 cases studied, and the fact that they did not appear suggests the rarity with which the average practitioner is likely to encounter them. However, in this clinic, peripheral fields are not performed routinely on ophthalmoscopically visible retinal detachments. For some of these cases the perimeter might be used, but only when clinical judgment dictates.

Only 25 fields (0.812% of total paired fields) on the 22 patients (1.16% of total patients) demonstrated negative central and positive peripheral fields, although possibly other similar series might show different findings. In not one case did the peripheral fields provide anything vital or in any way assist in the management or diagnosis of the case.

Summary

In this presentation we have attempted to remain as completely objective as possible, neither to condemn nor to condone the routine use of perimetry for field testing but rather to assess the relative value of perimetry in the office of the average ophthalmologist, i. e., attempting to determine when perimetry should be employed and when it may safely be omitted.

The abolition of perimetry is certainly not advocated; however, the real value of the routine use of peripheral-field testing is questioned.

On evaluation of the information presented, the impression is gained that perimetry might better be used much more selectively rather than as a routine procedure for screening purposes, since of the 25 paired fields which showed negative central and positive peripheral fields (out of a total of 3078 paired fields), several were readily explained by obvious conditions, such as a pterygium and cortical cataracts. The impression is also gained that the remainder of these 25 cases could have had central fields only and missed nothing important, since the peripheral fields contributed little or nothing to the diagnosis, treatment, or prognosis.

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Lacrimal Air Anomalies

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It is a curious fact that air, except in minimal amounts, is not often found in the lacrimal sac, despite its anatomic connection with the nose. One of the earliest tests (1823) for patency of the lacrimal passages was to have the patient blow the nose and feel or hear the exit of air from the lacrimal puncta; this, however, does not hold in most persons. According to Duke-Elder,[1] about 5% of persons can whistle through their eyes, as it were, when air is forcibly exhaled with the nose closed, and some can emit smoke in the same manner.

The nasolacrimal duct is an irregular passage lined with mucous membrane which has a variable number of folds, or valves, the function of which is uncertain. The fold at the lower orifice of the nasolacrimal duct, known as the valve of Hasner, is thought to be a barrier to the entrance of air and retrograde fluids from the nasal cavity. When there is a dysfunction of the valve, air may be blown into the tear sac. In some cases air enters the sac and is trapped there, forming a pneumatocele. If the nose is then blown strongly with the nasopharynx closed (this is done by saying "NG" silently), the sac becomes further distended. This may also occur on forced expiration with closure of nose and nasopharynx. Tearing may then result from malfunction of a dilated, atonic tear sac. The impaired drainage of tears may lead to stasis and secondary infection from the nasal secretions blown into the sac. Incompetency of the valve of Hasner is usually of congenital origin, but it may also come about from accidental or surgical trauma involving the orifice of the nasolacrimal duct, or from nasal infection, especially in aged persons.

The management of these conditions is to caution the patient to blow the nose gently, one nostril at a time, at the same time pressing firmly on the tear sac area. The lacrimal sac may be massaged a few times daily. In the presence of infection, irrigation of the lacrimal passages and topical application of antibiotic solutions are advisable. If a persistent dacryocystitis is a complication or a large pneumatocele develops, dacryocystorhinostomy is indicated.

Report of Cases

CASE 1.—A 13-year-old girl, daughter of a physician, consulted one of us (J. M. L.) in October, 1957, with the complaint of inconstant tearing of the right eye, especially when laughing or coughing, of a few years' duration. There was no history of eye infection or trauma or of nasal disease. The globe and lids appeared normal. Palpation over the right lacrimal sac area disclosed a tiny compressible swelling invisible to the eye, with crepitation loud enough to be heard a few feet away. No fluid came through the puncta on pressure over the sac. Fluorescein solution dropped into the eye was not transmitted into the nose. Irrigation through the lower canaliculus was exceptionally free into the nose. When she blew her nose forcibly with nostrils occluded, the tiny swelling, or pneumatocele, sometimes enlarged. Ear, nose, and throat study by the late Dr. David J. Morgenstern was negative. X-ray of the paranasal sinuses was negative. On dacryocystography [2] (Dr. Joseph J. Sher) of the affected side (Figs. 1, 2, and 3) the lacrimal tract was well visualized; the sac was overfilled; the system was patent; there was delayed emptying

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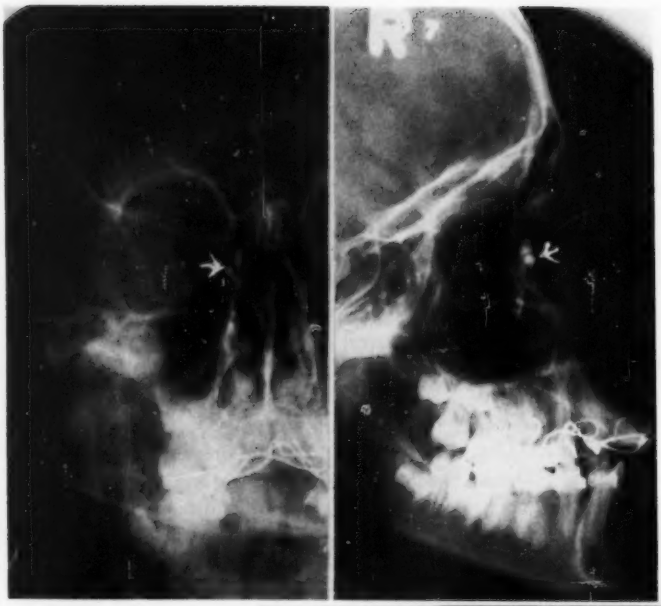

Fig. 1 (Case 1).—Posteroanterior and oblique views of the right lacrimal tract seven minutes after injection of the dye. The arrows point to the cystic diverticulum of the sac.

Fig. 2 (Case 1).—Posteroanterior view of right lacrimal tract 30 minutes after injection of dye. The entire lacrimal system and diverticulum are clearly outlined.

Fig. 3 (Case 1).—Same view two hours after injection of dye. The diverticulum retains the dye, while the lacrimal system is empty.

of the dye from the nasolacrimal duct (after two hours traces were still evident); the unusual finding was a diverticulum consisting of a sac and a narrow neck which joins the system at the lowermost position of the normal sac and is located slightly anterior and lateral to the sac; the diverticulum retained the dye almost completely after the lacrimal system had emptied.

This patient probably has two congenital anomalies, one at each end of the lacrimal tract: valvular insufficiency and a cystic diverticulum of the sac. It is also possible that the initial condition was congenital valvular insufficiency and that a diverticulum subsequently developed in a weak area of the sac wall as a result of forcible inflation. The diverticulum may be considered a factor in causing the tearing by exerting pressure or traction on the sac. However, since there is a marked functional block in the drainage of tears, excision of the diverticulum alone would not relieve the tearing. Dacryocystorhinostomy was advised, but the parents feel that the symptoms are not sufficiently distressing at present to warrant surgery.

CASE 2.—A 36-year-old female medical technician was seen by one of us (D. K.) in November, 1957. She said that her left eye had been tearing for three months and that when she blew her nose fluid, bubbling like soda water, came into her eye. There was no history of eye infection or trauma

Fig. 4 (Case 2).—Air bubbling from the lower lacrimal punctum of left eye when the nose is blown.

or of nasal or sinus disease. She demonstrated in the office a profusion of air bubbles along with clear fluid issuing from the lower lacrimal punctum when she blew her nose (Fig. 4). There was no visible swelling of the lacrimal sac. Loud crepitations were occasionally heard on palpation of the sac. Fluorescein solution dropped into the eye was not transmitted into the nose. Irrigation through the lower punctum was very free into the nose.

Ear, nose, and throat consultation by Dr. David J. Morgenstern revealed the following: Fluorescein solution instilled into the left eye is readily recovered in the lower end of the nasolacrimal tract only on downward massage of the tear sac; there is a septal spur on the left side of the nose where mucoid discharge is visible; the impression is that of left catarrhal antritis and ethmoiditis. X-rays of the paranasal sinuses were negative.

Dacryocystography (Fig. 5) of both sides showed the lacrimal tracts well visualized and patent. The right side gave a normal configuration and a normal emptying time for the dye; there was residual dye in the left tract after 45 minutes, and there was a marked distention of the left sac and nasolacrimal duct to more than twice the size of the normal right shadow.

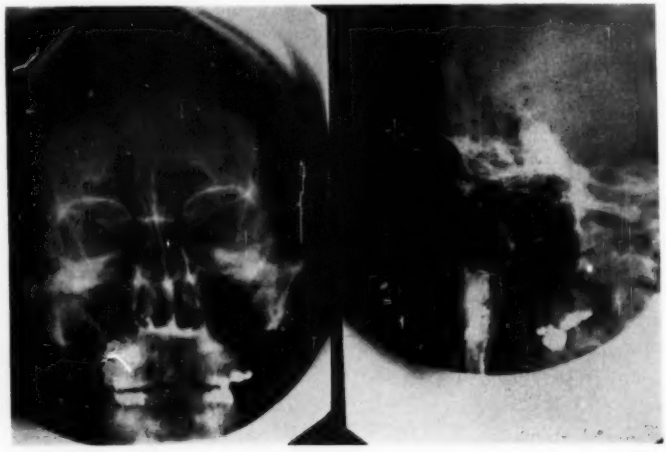

Fig. 5 (Case 2).—Posteroanterior and oblique views of both lacrimal tracts shortly after injections of dye. The left shows a marked overfilling of sac and duct, in contrast to the normal right tract.

This patient has incompetency of the valvular mechanism of the nasolacrimal duct, permitting air to be blown directly into the eye. Added to this, there is an element of infection from the nasal secretions. She was cautioned to blow her nose gently, one nostril at a time, while pressing firmly on the lacrimal sac area. Agnello[3] in 1937 reported an analogous case which cleared entirely with this conservative treatment. The lacrimal passages were irrigated once with a solution of chloramphenicol (Chloromycetin), and the same solution was prescribed for topical therapy. The patient reports freedom from all symptoms, including tearing, for the last four months.

Summary

Two cases of lacrimal air anomalies are reported. A 13-year-old girl has a tiny pneumatocele of the lacrimal sac and a cystic diverticulum of the sac. A 36-year-old woman emits air bubbles from the lacrimal punctum when she blows her nose. The appearance of air in any significant quantity in the lacrimal tract signifies defective valvular function of the nasolacrimal duct, usually of congenital origin. Air may be blown directly into the eye or may be trapped in the lacrimal sac, forming a pneumatocele. The lacrimal tract is patent. Epiphora results from malfunction or infection of a dilated sac.

Dr. Joseph J. Sher cooperated in doing the dacryocystography.

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Studies on Intraocular Effects of the Orbital Parasympathetic Pathway

I. Technique and Effects on Morphology

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Interest in the role that the nervous system may play in influencing the intraocular pressure or in providing a regulatory mechanism of intraocular fluid dynamics is by no means recent; nor is the interest in the effect that the act of accommodation or, more precisely, the contraction of the ciliary muscle may have on these parameters. Various hypotheses and generalizations from indirect evidence have been offered. However, definitive evidence has been, in general, lacking.

In recent years, a marked revival of interest in this area has become manifest; numerous workers have attempted investigations of this field, utilizing the various refinements in techniques of experimentation that have become available.

It would be to no advantage to survey the vast literature relevant to this subject or to emphasize the evident value of definitive information in this area and its importance in advancing our understanding of certain aspects of ocular physiology in general and the problem of glaucoma in particular. It would suffice to quote Duke-Elder's [1] summary of the results of different investigators in the last quarter of the 19th century: "That accommodation has no influence on the intraocular pressure was established by the early investigators both in the freshly excised eye and by stimulating the ciliary ganglion in the intact animal."

The results of recent work on the effect of the parasympathetics on intraocular pressure are by no means uniform. Schmerl and Steinberg [2] studied the effect of electrical stimulation and cauterization of the ciliary ganglion in the rabbit, with use of a needle electrode directed toward the ganglion at the apex of the orbit. They reported a rise in intraocular pressure on stimulation and a reduction on cauterization of the ganglion. Greaves and Perkins [3] studied the effect of electrical stimulation of the intracranial portion of the third nerve in the cat and reported a rise in intraocular pressure on stimulation which disappeared after an adequate dose of decamethonium iodide. They concluded that the parasympathetics had no influence on the intraocular pressure. The effect of electrical stimulation of various areas of the midbrain of the cat was studied by von Sallmann.[4] He succeeded in recording an occasional reduction in the intraocular pressure not associated with a reduction in the systemic blood pressure on stimulation of the parasympathetic area of the midbrain. These records stood as a serious challenge to the hypothesis that the effect of the nervous system on intraocular pressure is secondary to its effect of the systemic circulation. They pointed toward a "nervous effect" which should be explained by a primary ocular event rather than a consecutive secondary manifestation.

Purnell et al.[5] studied the effect of electrical stimulation of the "autonomic nerves" on the intraocular pressure in the enucleated

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perfused eye of the cat, and they reported a slight rise in pressure on stimulation and an increase in the rate of flow. They concluded that stimulation of the autonomic nerves in the enucleated eye increased the facility of outflow.

Armaly and Burian [6] utilized tonography in the study of the effect of accommodation and relaxation on intraocular pressure in young human subjects. They demonstrated that in young normal subjects the act of effortless accommodation produced a significant reduction in intraocular pressure. Furthermore, C-values of tonograms obtained during effortless accommodation were significantly larger than C-values of tonograms obtained on the same eye during relaxation.

The lack of harmony in the results obtained by different workers in this field seems to emphasize the importance of technique and preparation in investigating an area where multiple variables are capable of influencing the result, making definitive interpretation difficult. This has prompted me to seek a preparation wherein the "parasympathetics" are least confused and could be effectively isolated and their central as well as peripheral extraocular connections completely severed so that an electrical stimulus applied to this pathway would produce effects limited to the intraocular structures and accounted for only by intraocular events.

The value of such a preparation would be to provide an opportunity whereby the effect of stimulation of the most peripheral limb of the parasympathetic effector is studied in a preparation that lends itself to a definitive interpretation of results and analysis of mechanisms of action.

The experimental animal used was the cat. Preliminary experiments to procure such a preparation in the rabbit met with complications difficult to avoid because of the abundance of large thin-walled venous sinuses in the apex of the orbit surrounding the site of location of the ciliary ganglion.

In these studies a controlled electrical stimulus was applied to this isolated parasympathetic path to simulate a parasympathetic stimulation as gauged against known "parasympathetic" intraocular effects. The effect of such stimulation on the anatomy and morphology of intraocular structures, on the intraocular pressure, on the resistance of the outflow channels, on the intraocular vascular bed, and on the elasticity of the eye ball was studied in 140 experiments performed on 75 cats. The results of these experiments demonstrated that such stimulation is capable of producing marked changes in the items studied, and the results of this part of these studies will be the subject of this and future publications.

Technique and Preparation

A vertical skin incision was made just in front of the base of the pinna and extending superiorly to 0.5 cm. lateral to the midline of the skull and inferiorly 1 cm. below the zygomatic arch. The incision was then extended horizontally from both ends and the skin flap freed and reflected forward to the rim of the orbit and excised just lateral to the outer canthus.

The zygomatic arch was then severed at its ends and completely removed. The median bony wall of the temporal fossa was laid bare by reflecting all the muscular attachments to its periosteum, starting superiorly with the fan-shaped attachments of the temporalis muscle and carefully freeing the fibers inferiorly that form the outer boundary of the apex of the orbit by means of a muscle hook. The upper ramus of the mandible was then identified in the muscle mass and excised with a bone rongeur, thus facilitating the complete excision of the muscle mass forming the lateral boundary of the orbit. The mouth was then forced open maximally and maintained in this position by placing an appropriate length of wooden applicator between the upper and lower jaw. This maneuver was found to be extremely helpful in increasing the accessibility of the posterolateral segment of the orbit by re-

moving the upper ramus of the mandible and the remaining muscle attachments away from the field.

The fibrous tunic enclosing the globe and muscles was then incised horizontally, and the incision was carried posteriorly as far as possible, avoiding injury to the veins in this area. Tennon's capsule was then grasped and incised horizontally close to the lower border of the lateral rectus; the mass of fat lying between it and the inferior rectus was carefully excised. The incision in Tennon's capsule was extended as far back as possible, taking care to avoid the large vessels at the apex of the orbit. The inferior rectus was then identified; on the lateral one-third of its upper surface the nerve to the inferior oblique was easily identified, running medial to a large vein which could be avoided by blunt separation of the nerve from the surrounding tissue. The nerve was then cut and traced back with blunt dissection to the apex of the orbit, taking care to avoid the blood vessels in this area; posteriorly the nerve led to the ciliary ganglion, where it formed an integral part of that structure, thus making it possible to free the ganglion without unnecessary trauma. The ganglion was then separated from the inferior rectus and lifted to show further attachments to the proximal one-fifth of the inferior rectus. At least three such nerve trunks could be easily identified connecting the ganglion to the inferior rectus; these were severed. The ganglion then hung freely with only three trunks: a proximal one that could be traced from the proximal end of the ganglion to the third nerve at the apex of the orbit and two that left the distal end of the ganglion to course medially, gaining access to the optic nerve through an ill-defined conical muscle mass that surrounded the optic nerve and the posterior segment of the globe and lay within the striated muscle cone; they then coursed on either side of the nerve until they entered the eyeball through the perforations around the optic nerve attachment to the globe. The trunks were of unequal size, an anterior slender branch and a posterior stout trunk, both of which broke down into smaller branches to enter the posterior pole of the globe. Several fine branches stemmed from the ganglion and connected with the conical muscle mass that surrounded the optic nerve lying in the apex of the orbit. When all these connections were cut, leaving the preganglionic trunk and the two postganglionic trunks, stimulation of any part of this pathway led only to intraocular effects, and no visible muscle twitches or change in position of the globe or of any extraocular structure were seen.

In this preparation, once the proximal trunk was cut, the ganglion could be pulled laterally without undue tension away from the muscle cone for at least 2 to 4 mm., where an electrode could be applied without getting in contact with other structures.

In order to expose the superior cervical ganglion, the carotid sheath was exposed, and the superior cervical ganglion was identified in the carotid trigone as a spindle-shaped structure lying medial to a similar structure together with which it was enclosed in a fibrous capsule. Identification was further ascertained by mechanical and electrical stimulation of this structure correlated with dilatation of the pupil and retraction of the nictitating membrane; similar stimulation to the lateral structure resulted in vagal effects on the heart only. Once identified, the medial ganglion was completely separated from the lateral structure by blunt dissection of the fibrous capsule that encircled both; it was then resected in its entire length. Bilateral resections were performed simultaneously.

All experiments were performed under pentobarbital (Nembutal) anesthesia; 20 to 25 mg. per kilogram was given intrapleurally. Adequate surgical anesthesia ensued in 10 to 15 minutes.

Equipment

The operating table used had a V-shaped trough of stainless steel rods 5 cm. apart which formed the floor; to these rods stand-

ard C-clamps could be attached, and through the clamps a head-holder, and electrode manipulator, an I. V. infusion set, and pressure transducers could be affixed readily in any desired position. The table and the animal were grounded. The head-holder was designed so that the head was fixed in position by placing the upper and lower jaw in between movable horizontal bars that helped to fix the head as well as to maintain the desired opening of the mouth.

The electrode manipulator consisted of five arms attached to each other by double joints placed in opposing planes so that any desired position could be easily reached and maintained by the electrode held firmly by an alligator clamp fixed to the tip of the last arm of the manipulator.

Two electrodes proved most satisfactory for this study. One consisted of two 4 in. stainless-steel needles that moved freely, one inside the other, after insulation. The inner needle was a 22 gauge needle insulated by a polyethylene tube that exposed 1 mm. of the tip, covered the entire length of the needle, and fanned out to cover the butt. The outer needle was a 13 gauge needle in which the tip was filed into a plane surface 1.5 mm. in width and 5 mm. in length; this was bent like a fish hook towards the lumen of the needle with a horizontal arm 2 mm. long and a vertical arm 3 mm. long. Insulation of the outside of the needle was achieved by a polyethylene tube that covered the butt, the shaft, and the outer surface of the hook to its tip and was fixed in position by heat. A fine threaded wire was soldered to the butt of each needle underneath the plastic insulation so that the only passage of the current was between the tip of the internal needle and the internal surface of the hook of the outer needle. The ganglion, 2 mm. in diameter, could be conveniently hooked, and the internal needle would then be allowed to pierce it (Fig. 1).

The second electrode consisted of two stainless steel wires 1 mm. apart embedded in an acrylic rod 2 mm. in diameter. At one end these wires projected 1 mm. outside the acrylic rod, and their ends were sharpened to a needle point. At the other end the plastic rod was enlarged to fit snugly the inner diameter of the needle butt, so that it could not be pushed beyond a certain point. From this end the wires projected loose so that connections could be made between them and the stimulator. This plastic rod could fit very freely in the 13 gauge needle mentioned previously which, in this case, was used only for mechanical support. When the plastic rod was pushed maximally, it left a space 1 mm. wide between the tips of the wires and the inner

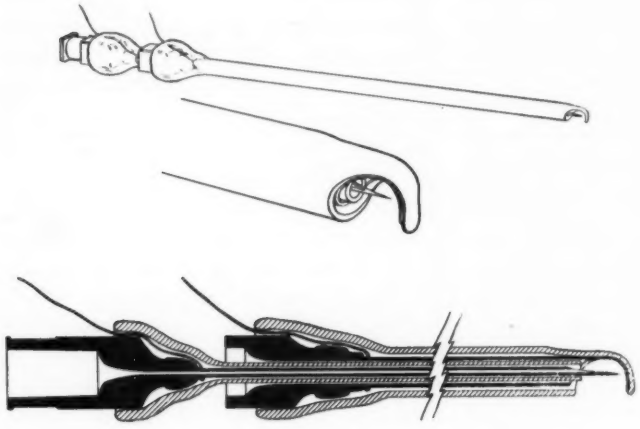


Fig. 1.—Bipolar electrode No. 1. Stainless steel needles in solid black; plastic insulation in stripes.

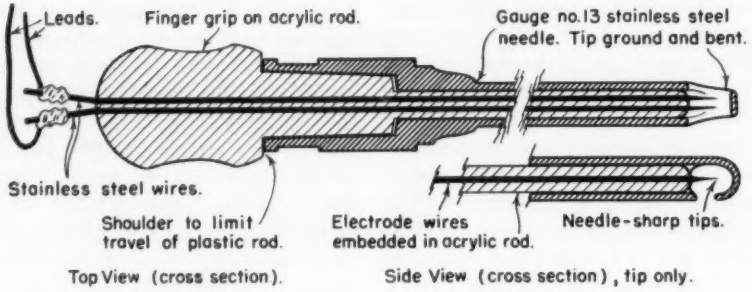

Leads.
Finger grip on acrylic rod.
Gauge no.13 stainless steel needle. Tip ground and bent.
Stainless steel wires.
Shoulder to limit travel of plastic rod.
Electrode wires embedded in acrylic rod.
Needle-sharp tips.
Top View (cross section).
Side View (cross section), tip only.

Fig. 2.—Bipolar electrode No. 2.

surface of the inverted hook of the needle (Fig. 2).

These electrodes were clamped with the alligator clamp at the tip of the manipulator. The wires were connected to the output switch of the generator.

A Grass square-wave generator, Model S4C, was used to supply a controlled stimulus. The following were the characteristics controlled: frequency, delay, duration, voltage, pulse, phase, and polarity.

Intraocular pressure records were obtained from a Model P32B Statham transducer and a Model 267B Sanborn pressure transducer connected through a polyethylene tube to a 26 gauge needle shaft connecting it to the anterior chamber. Heparinized saline was the fluid used to fill this system; it was prepared by adding 0.5 cc. of heparin to 100 cc. of saline. The use of this solution eliminated the interference in the patency of the system that resulted from fibrin flaps formed at the top or in the shaft of the needle. No solution was injected into or removed from the anterior chamber except when so indicated. An 18 gauge needle shaft was used for the vitreous chamber and a 26 gauge needle shaft for the posterior chamber. Pressure gradient was measured by a Model 267B Sanborn differential pressure transducer; the same transducer was used to obtain a record of intra-arterial pressure.

The signals of the pressure transducers were transferred to a paper record through a Sanborn carrier-amplifier and recorder.

Experimental Procedure

Bilateral superior cervical sympathectomy was performed two to four weeks prior to the experiment. Experiments were performed on tracheotomized cats that could be placed on artificial respiration when indicated. This was needed only in curarized cats.

The pressure-recording equipment was calibrated against a known external pressure at the beginning of every experiment. No loss of aqueous, change in depth of the anterior chamber, or injury to the iris was encountered in any of the experiments performed on the 140 eyes to be reported.

Once the ciliary ganglion was exposed on both sides and all connections other than the pre- and postganglionic trunks mentioned previously were cut, the cat was placed in a horizontal position with the mouth maintained opened by the horizontal bars of the mouth holder clamping the upper and lower jaw and fixing the head so that the eyes were horizontally pointed, about 5 cm. above the longitudinal midline of the body, with no undue stretching of the neck.

The anterior chamber was then cannulated with the 26 gauge needle shaft leading to the closed system of the transducer. The arterial pressure was recorded from the abdominal aorta with a polyethylene tube cannulating the femoral artery or from the common carotid artery when observations of the eye on the same side were over.

Effect of Sectioning the Central Connections

After the surgical intervention, there was no change in the conjunctival or limbal vessels, the corneal luster, the transparency of the aqueous, the character of the iris and pupil, or their reaction to light when such changes were looked for through the slit lamp. The eyes maintained this appearance for three to four hours in general, after which a slight turbidity became apparent in the aqueous; during this time the cornea, if kept moist, did not change its characteristics; the reaction of the pupil became sluggish to light, and the components of the major circle of the iris became visible.

When the central connections were cut, leaving a 4 to 6 mm. piece of the preganglionic fibers (the part of the third nerve proximal to the ganglion), the following observations were made: Through the slit lamp no change could be discerned in the conjunctival vessels, limbal vessels, aqueous, or aqueous-carrying veins. The vessels of the major circle of the iris became more prominent and their pulsation more readily visible.

The main changes were observed in the pupil, iris, anterior chamber, anterior surface of the lens, and intraocular pressure.

The pupil instantaneously dilated from a vertical slit to become circular, 8 to 10 mm. in diameter.

The iris became accumulated in the peripheral 2 mm. of the chamber with an apparent forward movement, resulting in a reduction of the distance between its anterior surface and the posterior surface of the cornea and a reduction in the angle formed by these two structures, when observed gonioscopically. Exact measurements of the change in the plane of the iris were not made, but such changes could be appreciated through the slit lamp.

The anterior surface of the lens, once in sharp focus, became out of focus after sectioning of the central connections, and the slit lamp had to be moved forward in order to bring the same area in focus, indicating a definite increase in the distance between the central part of the posterior corneal surface and the central part of the anterior surface of the lens. Here, again, no exact measurements of this distance were made, but the change was of such magnitude that it could be readily appreciated.

The anterior chamber, as a result, was significantly deeper after resection of the central connection, and this depth was significantly more than the thickness of the stretched iris leaf.

Sectioning of the central connections produced no change in arterial pressure or in the intraocular pressure of the opposite eye in this preparation when such a change was looked for for 20 to 30 minutes.

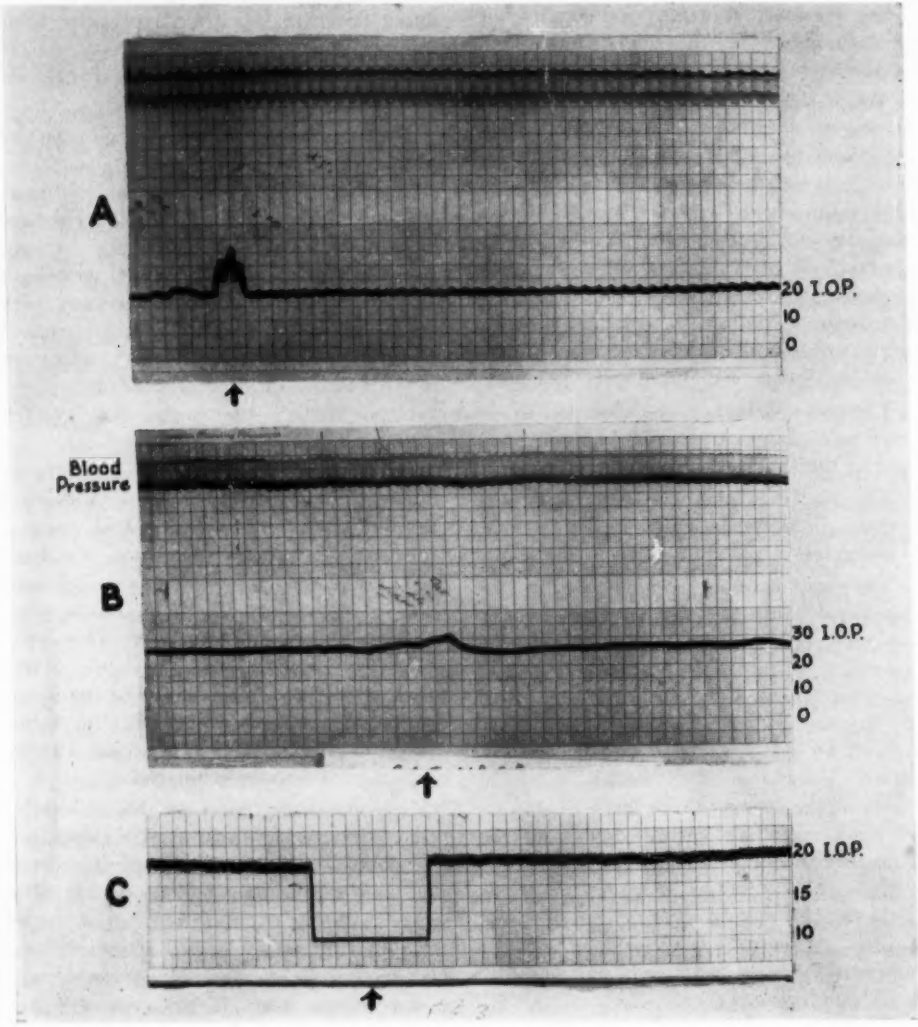
The significant pressure change occurred in the eye of the same side. In general, the intraocular pressure after the surgical intervention started above 13 mm. Hg and reached as high as 25 mm. Hg in some preparations. It is difficult to tell how much was the effect of the interference with venous return in the extensive anastomosis that exists between the orbital circulation and that of the extraorbital structures which were removed in order to gain access to the ganglion.

The effect of sectioning the central connections was studied in the following manner: The eye was allowed to reach a steady state of intraocular pressure following cannulation, and when this pressure level was maintained for 10 minutes or more the resection was performed. This procedure required retraction of the lateral rectus and a pull on the stump of the nerve to the inferior oblique in order to bring into view the preganglionic trunk, which could then be severed with scissors.

To evaluate the effect of this manipulation on intraocular pressure, the procedure was done several times without the actual sectioning of the preganglionic trunk. The pressure during manipulation, which lasted one to two minutes, showed spurious rises, then went back to the original level, and stayed at that level. If, however, the pre-

ganglionic trunk was sectioned, the pressure did not go back to the original level, but it resumed a new higher level in the vast majority of the experiments. The magnitude of the rise was, on the average, between 1 and 3 mm. Hg, but it reached as high a value as 5 mm. Hg in certain preparations. This rise was maintained for a variable period of time, from 1 to 20 minutes, before recovery of the previous pressure level was attained, without any associated change in arterial pressure, as was mentioned. This change in intraocular pressure on sectioning the preganglionic trunk occurred in previously sympathectomized as well as in nonsympathectomized eyes (Fig. 3).

Fig. 3.—Effect of sectioning the central connection of the preganglionic trunk of the ciliary ganglion on intraocular pressure. Arrow indicates time of intervention. *A* and *B*, upper tracing: record of blood pressure before, during, and after sectioning; lower tracing: record of intraocular pressure in mm. Hg before, during, and after sectioning. *C*, tracing of intraocular pressure before and after sectioning in mm. Hg.



The Effect of Stimulation of the Orbital Parasympathetic Pathway

1. *Minimum Effective Stimulus.*—In order to determine the strength of the electric current to be used for evaluation in this study of the "parasympathetic" effect on intraocular pressure, certain criteria had to be set as representing a "parasympathetic effect." These were as follows: effect on the pupil, effect on refraction, and effect on intraocular pressure.

A. The Effect on the Pupil: A change in the size of the pupil was looked for with the naked eye, starting from zero voltage and gradually increasing the voltage until a change could be discerned. The strength required to produce the first noticeable change in the diameter of the pupil was considered to be one of the parameters of the minimum effective stimulus. The strength varied between 0.75 and 3 volts from one preparation to the other. The other characteristics of the stimulus were frequency of between 10 and 50 cycles per second, delay of 0.01 milliseconds and a duration of 1 to 10 milliseconds, delivered as a biphasic pulse from the square-wave generator described previously.

The change in sympathectomized cats was a constriction of the pupil. Variation in the frequency and delay did not seem to influence the quality or the magnitude of the response to the minimum effective stimulus in a significant consistent manner. No increase in the diameter of the pupil was observed in the previously sympathectomized cats. It was observed only in cats in which no previous sympathectomies had been done, and it seemed to be related to the strength of the stimulus used and to the position of the electrode; the dilatation occurred with weaker stimuli. For the same strength of stimulus, a change in the position of the electrode was enough to reverse the response from a dilatation to a constriction.

At this level of sensitivity of observation, it was concluded that constriction of the pupil was the change that should be looked for in assessing the beginning of parasympathetic effect and that the occasional dilatation in the nonsympathectomized cats and its behavior were due to stimulation of the sympathetic fibers that coursed through the ciliary ganglion. This will be elaborated on at a later stage.

It is proper at this stage to mention that, while in general the constriction was uniform, involving the whole circumference of the pupil more or less equally, a constriction of one-half or one sector only was occasionally encountered; this would remain despite the increase of the voltage by severalfold, but would disappear when the position of the active electrode was changed.

B. Change in Refraction: Another component of a "parasympathetic effect" was the change in refraction. This was looked for with the help of the streak retinoscope. A neutralization point was found before and after a stimulus was applied. In general, this procedure was complicated by the induced corneal astigmatism because of the distortion by the needle. Yet, by observing one meridian and limiting the observation to the central part of the lens, one could detect a difference of 0.5 D. as a significant change in refraction. Such a change was induced by a current voltage that varied from 1 to 3 volts, keeping the other characteristics of the stimulus as before. At times a change in refraction of 1 D. was obtained without any noticeable change in the pupil size to the naked eye. This change increased with the strength of the stimulus to as high as 6 D., but within the range of the stimulus strength used for investigating pressure effects it ranged between 1 and 2 D.

Attempts at evaluating the change in refraction before and after sectioning of the parasympathetic trunk were not very rewarding because of the slit pupil before sectioning.

Since the same range of strength was effective for both these criteria of parasympathetic effect, the pupillary constriction was chosen for convenience.

C. Effect on Intraocular Pressure: This response was by no means a known "para-

sympathetic effect"; its inclusion in the list of candidate factors for gauging the minimum effective stimulus would appear unwarranted. However, this was adopted later when it became evident that this effect was as much a parasympathetic effect as any mentioned above.

A reduction in intraocular pressure on stimulation that exceeded significantly the rhythmic change due to circulatory and respiratory waves was considered as one of the factors against which the strength of the minimum effective stimulus could be gauged.

In the beginning of the study, a unipolar electrode was used, and the response of the intraocular pressure was varied, unpredictable, and associated with extraocular muscle contraction, movement of the eye, change in arterial pressure, and pressure in the opposite eye. Thus one could not tell whether the change in pressure was due to extraocular factors or to intraocular effects, or which change was due to which factor. However, once the connections of the ciliary ganglion to the inferior rectus, as well as its connections to the retrobulbar muscle mass, were observed and severed, and the unipolar electrode was replaced by one of the well-insulated bipolar electrodes described above, the pressure response became characteristically uniform and predictable with the highest degree of confidence.

This pressure response occurred with the same characteristics of the stimulus mentioned previously and with a magnitude of 0.75 to 3 volts. Its uniformity and its occurrence at times unaccompanied by a noticeable change in the size of the pupil and its absence on occasions where a marked pupillary constriction had occurred justified its inclusion as a response which can serve as a criterion of the minimum effective stimulus.

It was found that, in general, despite the difference in the relative sensitivity of detecting change in these responses (the naked eye for the pupil size, the retinoscope for lens changes, pressure transducers for intraocular pressure), significant changes were detected at the same level of strength of the stimulus. It was not possible to separate these responses by varying the characteristics of the impulse shower when this shower was delivered at the same voltage level. It was possible to change one or more of these responses by increasing the voltage or by changing the position of the active electrode.

This seems to point out that in this preparation, as would be expected, the effect of a stimulus was limited to a certain group of neurons or fibers that innervated only a segment of the parasympathetic effector organs and that the different segments could be brought to action by the same stimulus if the positioning was favorable.

The "minimum effective stimulus" was determined for every preparation; it varied from one to another in the above-mentioned range and it varied in the same preparation in time. This rate of change was fairly slow but gained speed after the second or third hour.

2. *Determination of the Strength of the Working Stimulus.*—Once the "minimum effective stimulus" was determined for a preparation, the problem of a "range of working stimulus voltage" was investigated by looking for effects other than those mentioned for the eye on the same side. The following were the changes looked for: movement of the eyeball, contraction of the extraocular muscles, movement of the head or trunk, change in arterial pressure, and change in intraocular pressure of the opposite eye. It was found that the voltage could be increased from the strength of the minimum effective stimulus up to 20 or 30 volts before any of these changes became manifest. Of these, the earliest were changes in the arterial pressure and twitches of the extraocular muscles on the same side.

Needless to say, during this increase in voltage, the magnitude of the response in the eye on the same side became progressively greater.

With this information, it became possible to conclude that "electrical leak" below this range of voltage was ineffective and a working voltage could be chosen within this

range which would stimulate a part of the "parasympathetic" path. The working voltage chosen for investigation varied between 3 and 5 volts, unless an increase was indicated in investigating the effect of a certain factor.

This working voltage induced a change in refraction that varied between 1 and 2 D. and caused a reduction in the pupillary diameter of 2 to 5 mm. from the dilated position.

The investigation of this working range is important in another respect, since arterial pressure records were obtained simultaneously and a change in these records would have indicated a reevaluation of the set-up. Its importance lies also in the fact that it provided an idea as to "how much of a parasympathetic effect" we were obtaining from an electrical stimulus and how it compared with effects engendered by other means or under different conditions.

The magnitude of parasympathetic effects on the pupil and refraction in this preparation was not beyond what could be engendered by other agents, nor was it outside the range of what the parasympathetic system is capable of doing during "ordinary" activity; it was much less than what "parasympathetic stimulation" could produce at maximum voltage before electrical leak became effective.

Effects of Stimulation on the Morphology of the Anterior Segment

1. *The Pupil.*—As was mentioned previously, the response was that of constriction of the pupil from the dilated position. At no time was a dilatation obtained in any of the 3500 stimulations in sympathectomized cats used in these studies. Dilatation did occur occasionally in 150 trials in nonsympathectomized cats. This seems to point toward a marked reduction in the effectiveness of the sympathetic pathway that courses in the orbital parasympathetic path following bilateral resection of the superior cervical ganglia. For in the nonsympathectomized cats similar stimulations, though much fewer in number, succeeded in producing a small number of responses with a predominance of sympathetic effect manifested in dilatation of the pupil.

While this is by no means to be interpreted as achieving a functional sympathectomy of the intraocular structures by resection of the superior cervical ganglia,[7] it indicates that this procedure has at least markedly increased the predominance of the parasympathetic effect when an electrical stimulus was applied to the orbital parasympathetic pathway and that the sympathetic effect which might also be engendered by such stimulation was definitely reduced and at no time reached enough magnitude to become the predominant effect, despite the significantly larger number of trials with random positioning of the electrode which should have elicited this predominance, if it were at all possible.

2. *The Lens.*—On stimulation, a very impressive change became apparent in the lens. A marked bulging forward of the central core of the anterior surface occurred with marked increase in convexity of this surface, so that it really approximated a cone. This change could be very well examined with the slit beam, especially when such a change was not accompanied by a marked constriction of the pupil, thus facilitating investigation of the periphery of the anterior surface.

This forward conical bulging was limited mainly to the central 6 mm. of the lens and was not detected peripheral to that (Fig. 4).

This resulted in reduction of the distance between the center of the posterior surface of the cornea and that of the anterior surface of the lens to one-half to one-third of the distance before stimulation. Here again, it was possible to obtain marked lens and refraction changes with minimal pupillary constriction. The maximum increase in refractive power during stimulation with increasing voltage was 6 D.

An interesting movement of the lens was that associated with the spiral movement of the iris and the pectinate fibers, to be de-

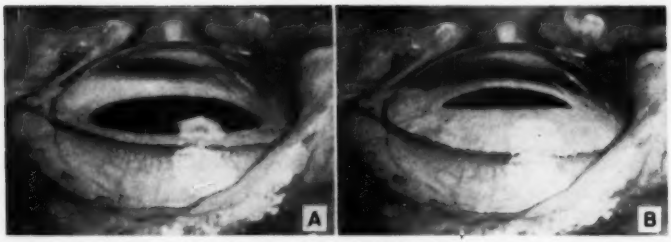


Fig. 4.—Photographs of the anterior segment. *A*, before, and *B*, during, stimulation of the ciliary ganglion. The eye and the camera had identical position during the two situations. An idea about the magnitude of the forward bulging of the central portion of the anterior surface of the lens can be obtained by comparing the distance between the center of the pupil and the center of the anterior corneal surface in the two photographs.

scribed later. In this movement the lens not only underwent the marked changes described for the anterior surface, but, in addition, it was tilted so that the anterior surface did not occupy a plane normal to the anteroposterior axis any more but rather a vertical plane tilted on the anteroposterior axis. This tilting occurred about the meridian perpendicular to that in which maximum recession of the ciliary body-iris insertion occurred. It was difficult to demonstrate whether the lens in addition underwent a circular rotation when this movement occurred, but an impression was obtained that this did happen.

3. *The Iris.*—On stimulation, pupillary constriction was the rule, but as mentioned previously, its magnitude was not always correlated with the magnitude of the other responses. It varied from complete absence to very forceful constriction running parallel to the magnitude of the other responses. It also varied from a constriction of a quadrant or half to a uniform circular constriction.

This constriction brought down the iris leaf over the forward-bulging conical anterior surface of the lens, so that it became a truncated cone whose apex was the pupil and whose base was at the junction between the central three-fourths and the peripheral one-fourth of the iris. The estimated distance between the apex and the base reached as high as 2 mm.

While the central three-fourths now occupied a more forward plane, tangent to the new plane of the anterior lens surface, the peripheral one-fourth underwent a marked displacement in the opposite direction. A marked forceful backward recession of the peripheral one-fourth of the iris occurred, so that it became a concave trough 2 to 3 mm. wide and 1 to 1.5 mm. deep, usually circular and uniform, involving the entire circumference, but variation in depth in different areas of this circular trough were observed.

As a result a marked increase in depth of the chamber angle was observed due to the quick and forceful backward recession of the plane of the ciliary body-iris attachment during stimulation.

This increase in the depth of the chamber angle continued to occur when stimulation was applied after the pupil was brought down to a hardly visible slit by perfusing the anterior chamber with pilocarpine.

Furthermore, this increase in depth occurred when the pupillary constriction from the dilated position was minimal and the change in refraction was the predominant component of the response.

Observation of the vessels of the major circle of the iris revealed that on stimulation there was a sudden cessation of pulsation which became visible but greatly reduced in volume after 15 to 60 seconds of maintained stimulation.

A rather peculiar change in the iris, pupil, and chamber angle was occasionally encountered, which was better seen than described, since it involved positional

changes in three planes. It is best described as a spiral movement. If one visualizes a cross in the plane of the iris, with its ends at the chamber angle at the site of the iris-ciliary body attachment, then, on stimulation, one or more ends of the cross describe a circular displacement. This displacement was more often counterclockwise than clockwise in direction. At the same time, these same ends of the bars would be pulled backward away from the surface of the cornea, resulting in marked increase in the distance between the ciliary body-iris insertion and the posterior surface of the cornea.

As a result, the ends of the cross which previously occupied one plane now were distorted so that two or more ends became closer to each other and these displaced ends occupied a more backward position than the remaining ones. At times, this spiral movement involved all the circumference of the ciliary muscle-iris insertion area, and so this spiral backward movement, which could be increased by increasing the strength of the stimulus, gave the impression that the whole attachment to the chamber was to become disinserted.

It is in association with this spiral movement that tilting of the lens along the anteroposterior axis was observed and that the impression of rotation was gained.

Associated with this spiral movement and recession of the iris-ciliary body area was a displacement of the pupil so that it became eccentric and pulled toward the site of recession of the ciliary body-iris attachment. At first, because of this eccentric displacement, one obtained the impression of dilatation. However, careful examination revealed always a smaller pupillary diameter; this movement was not a dilatation but rather an eccentric displacement of a constricted pupil in the direction of the recessed ciliary body-iris attachment.

4. *The Pectinate Ligament Fibers.*—Of great interest and importance in interpretation were the changes observed gonioscopically in the pectinate fibers.

On stimulation there was an increase in the length of the visible portion of the pectinate ligament fibers. This increase was mainly due to the active recession of their attachment to the ciliary body and base of the iris. This increase in length was seen when the constriction of the pupil from the dilated position was minimal and the iris leaf remained crowded in the periphery of the chamber, as well as when the pupil was brought down to a hardly visible slit with pilocarpine.

With this increase in the visible pectinate fibers there was a definite evidence of increased tension in them. This increased tension was inferred from examining the area of their attachment to the iris-ciliary body region. This attachment became tented and so while the rest of the uveal tissue was actively pulled back, a cone of this tissue which was attached to the base of the pectinate fibers became prominent.

Another change in the position of the pectinate fibers could be appreciated by constant observation of a single sector. One could see a set of fibers in which one could visualize individual fibers situated one lateral to the other and in general two to four fibers in depth between the chamber and the corneoscleral junction. On stimulation one could see at times that the number of visible individual fibers increased and that the fibers became more separated from each other, the gain in distance being in the direction of the anterior chamber. This displacement of the pectinate fibers medially toward the center of the chamber occurred to a greater degree when marked constriction of the pupil was a prominent component of the reflex, especially the displacement of the most medial fibers. However, this movement was present when stimulation produced a minimal twitch in the dilated pupil and when the main component of the response was the ciliary muscle contraction, leading to changes in refraction.

Observation of the pectinate ligament fibers at the time when the spiral backward movement of the ciliary body-iris area occurred revealed that the pectinate ligament fibers participated in this movement and that their bases underwent a similar

rotatory movement in the same direction as that of the ciliary body-iris area.

5. *Volume of the Anterior Chamber.*—It is difficult to tell with certainty whether the total volume of the anterior chamber changed on stimulation and, if so, in which direction. While the central part of the chamber became markedly reduced, the peripheral part became markedly increased. The larger diameter of the periphery could account per unit change in depth for a significantly larger volume than the central portion.

Preliminary attempts at quick freezing of the eye in the stimulated state with liquid nitrogen met with considerable difficulties in final fixation. It is hoped that when these difficulties are overcome, such a preparation would provide more definitive information regarding the effect of stimulation on the volume of the anterior chamber.

Observation of the conjunctival vessels, aqueous, and aqueous-carrying vessels did not reveal any significant change during stimulation when such changes were looked for with the help of the slit lamp.

Observation of the retinal circulation with the ophthalmoscope revealed no significant changes. Such observations, however, were handicapped by the associated changes in refraction. No change in the retinal circulation was observed when the eye was opened and the posterior segment examined by direct inspection.

The changes described in the iris, anterior chamber, pectinate fibers, and lens during electrical stimulation of the orbital parasympathetic pathway were successfully recorded in a colored movie of these structures from which these changes could be observed and studied at will at different speeds.

Of the changes mentioned, constriction of the pupil and forward bulging of the central portion of the anterior surface of the lens require no further comment.

However, the behavior of the peripheral part of the chamber, the ciliary body-iris attachment, and pectinate ligament deserve further elaboration.

The question of what happens to the attachments of the ciliary muscle during accommodation is by no means recent. Evidence that the choroid is pulled forward during accommodation was presented by several investigators using various techniques.[8] However, the question of what happens to the anterior attachment has not been settled. The hypothesis that the scleral spur is pulled backward resulting in "opening up" of the angle has been more or less "formal."[9,10] Yet, evidence that this actually happened was still lacking.

In the human, Burian and Allen[11] observed an increase in depth of the chamber during accommodation and a recession of the periphery of the iris. Sugar,[12] on the other hand, observed that "the periphery of the iris came forward during accommodation and fell backward when there was no accommodation."

In these studies on the cat chamber, marked increase in the periphery of the chamber was the rule without a single exception, even when the depth of the chamber was changed experimentally.

The question of determining what causes this increase in depth was facilitated in the cat. It could be argued that this was brought about by the fluid displaced from the central portion of the chamber by the forward bulging of the lens and that the recession of the iris was brought about by the displaced fluid rather than by the active contraction of the ciliary muscle. In the cat the presence of pectinate ligaments that are readily accessible to examination through a gonioprism and the behavior of these pectinate ligaments on stimulation leave little doubt that the contraction of the ciliary muscle causes retraction of its anterior attachment to the meshwork and iris in a backward as well as a medial direction, causing an increase in the depth of the anterior chamber angle together with an increase in the area occupied by the posterior portion of the fibers, or fanning of these fibers toward the direction of the anterior chamber.

The fibrillar meshwork of the chamber angle is arranged in laterally placed sets in which the individual fibers of one are superimposed on the interfibrillary spaces of the other. This arrangement makes the lateral distance between one set and the other of critical importance in determining the size of the effective space available for fluid outflow and thus modifies the resistance to outflow offered by this meshwork. A reduction of this distance or lateral compression of this meshwork will act to increase the resistance, and fanning or an increase in lateral separation will act to reduce the resistance.

The geometry and spacial arrangement of this meshwork can be markedly influenced not only by actual positional change but also by the magnitude of "tension" developed in these fibers; for a given set of conditions, a greater "tension" will favor separation and reduction of the resistance, and a "reduced" tension will favor compression and an increase in the resistance.

Furthermore, by active recession of the forward extremity of the ciliary body-iris attachment in which the bases of these fibers are inserted, the spaces at the bases which are larger than those at the corneal apex now become available for fluid outflow, a measure which will also reduce the resistance.

If one were to take the liberty of inferring functional changes from these observable anatomical changes, the attachments of this fibrillar meshwork to the ciliary muscle become more critical in inducing change in the resistance of this meshwork than the attachment to the scleral spur. This influence would be predicted as an increase in facility of outflow on contraction of the ciliary muscle fibers, meridional as well as circular, and a reduction in this facility on relaxation. This was found to be the case in these studies and will be reported in following publications.

Summary

A preparation wherein the orbital parasympathetic pathway could be isolated from central and peripheral extraocular connections and to which an electrical stimulus could be applied and produce only intraocular effects on the stimulated side is described.

This preparation was used in 75 cats on which bilateral resection of the superior cervical ganglion was done two to four weeks previously to study the effect of electrical stimulation of this path on the morphology of the intraocular structures, the intraocular pressure, the resistance to outflow, the intraocular circulation, and the elasticity of the eyeball.

The details of the technique of investigation, the criteria utilized, and the equipment used in these studies are described.

The "minimum effective stimulus" and the "working strength of the stimulus" are defined. In this preparation the constriction of the pupil and change in refraction and intraocular pressure were the criteria used to determine the minimum effective stimulus. This ranged from 0.75 to 3 volts when delivered as a biphasic pulse at a frequency of 10 to 50 cycles per second, delay of 0.01 milliseconds, and duration of 10 milliseconds from a square-wave generator.

It was found that the voltage could be increased from this level up to 20 to 30 volts before signs of "electrical leak" became effective on extraocular structures of the same side, the intraocular pressure of the opposite side, the systemic arterial pressure, or the position of the head or trunk. The working stimulus voltage used for investigating the parasympathetic effect ranged between 3 and 5 volts.

On sectioning the central connection of the isolated parasympathetic path there was marked dilatation of the pupil, recession of the anterior surface of the lens leading to an increase in the depth of the central portion of the anterior chamber, a crowding of the iris in the periphery of the chamber angle, reduction in depth of the chamber angle, and an immediate rise in intraocular pressure by 1 to 3 mm. Hg which came down gradually to the initial pressure value in 1 to 20 minutes.

On stimulation of the parasympathetic pathway, there was a marked constriction of the pupil and a forward bulging of the central 6 mm. of the anterior surface of the lens, leading to a marked reduction of the depth of the central portion of the anterior chamber to one-half to one-third its original depth; the iris was pulled over the bulging lens surface assuming the appearance of a truncated cone; the pulsation in the vessels of the major circle ceased, then recovered at a much smaller volume in 15 to 60 seconds of maintained stimulation.

The peripheral one-fifth of the iris and the anterior base of the ciliary body were forcefully pulled backward and medially, resulting in a marked increase in the depth of the chamber angle, an increase in the tension in the pectinate fibers, and fanning, with increased separation of the adjoining layers of these fibers; the gain in distance was toward the center of the anterior chamber.

Occasionally a spiral backward movement of the ciliary body-iris attachment with eccentric displacement of the pupil and rotation of the base of the fibers of the chamber angle, as well as tilting of the vertical plane of the lens, was observed. A marked reduction in the diameter of the iris-ciliary body attachment was observed gonioscopically on stimulation.

No change was observed in the limbal, aqueous, or retinal vessels or in the optical properties of the aqueous humor.

It was concluded that bilateral superior cervical sympathectomy markedly reduced the effectiveness of the sympathetic pathway coursing in the orbital parasympathetic path to electrical stimulation and that at no time was it able to produce a detectable effect in these preparations.

These studies further provided evidence, seen directly through the gonioscope and recorded in a colored movie, that contraction of the ciliary muscle produces a backward and a medial retraction of its anterior attachment to the chamber fibers as well as iris insertion; this behavior was the rule without exception.

This action of the ciliary muscle, coupled with the intimate attachment of chamber fibers to meridional as well as circular fibers of the ciliary muscle, makes contraction or relaxation of the ciliary muscle capable of producing marked alterations in the geometry of the fibrillar barrier of the chamber angle; this is done not only by increasing tension in these fibers but, equally important, also by fanning of the fibers at their base of insertion, leading to separation of the laterally arranged sets of fibers and alteration of the arrangement of the fibers of one set in relation to those of another, producing marked changes in the resistance that this fibrillar barrier can offer to the outflow of aqueous.

That the state of "tension" of the ciliary muscle fibers influences the resistance to outflow will be reported in following publications.

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The Treatment of Congenital Dacryostenosis

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Although the arguments for early and late probing[1-8] of the nasolacrimal duct have been waged back and forth for several years, more and more ophthalmologists are adopting early probing as the treatment of choice for dacryocystitis secondary to congenital dacryostenosis in infancy.[9,10] It is my belief that this adoption is a relatively slow process because of the voluminous literature and teaching of the past to the effect that early probing is injurious to infantile tear ducts.[4,11-15]

Evidence is accumulating, however, that the opposite is true and that damage occurs only as a result of temporizing or deferring probing rather than by early probing and, moreover, that early probing, properly performed, is essentially innocuous and a curative procedure.[16-27] In order to add further to this evidence, this paper presents a comparison of experiences in series of both early and late probings that I have personally performed.

Early Probing

Cassady's excellent articles, which are classical in the presentation of the case for early probing, clearly outline the basic techniques for safe, adequate, and successful probing in infancy. During the past nine years, I have employed an almost identical technique in probing infants from 3 weeks to 3 months of age. Rather than outline my own probing technique, I would refer the reader to his presentations.[16,17] The principles of adequate immobilization, syringe-cannula instrumentation, and sufficient operative irrigation are well outlined there. My only addition is that, once the imperforate nasal ostium of the nasolacrimal duct has been punctured, I attempt to manipulate the tip of the lacrimal cannula gently, using the upper limit of the bony nasolacrimal canal as a fulcrum, so that the hole in the punctured membrane may be enlarged from that obtained with simple puncture.

With use of this technique in probing 53 youngsters (67 nasolacrimal ducts) between the ages of 3 weeks and 3 months, complete success has resulted in every case without the necessity of repeating the probing in any instance. In all patients, eye drops were prescribed for a few days to one week preoperatively and for one week postoperatively. Early in this series, sodium sulfacetamide drops were used, then sulfisoxazole (Gantrisin), and now a preparation of polymyxin B sulfate, bacitracin, and neomycin (Neosporin) is used. The prescribed drops were also used as the irrigating solution in all cases, being taken directly from the patient's bottle, and the nasolacrimal system was left filled with the solution during withdrawal of the cannula. Of course, these procedures were all conducted in the office with only local drop anesthesia being used. See the Figure.

Probing is extremely easy with all youngsters operated on in this manner, especially since no resistance is encountered until the tip of the cannula reaches the nasal ostium. Then, with gentle pressure, a soft "popping" sensation is felt as the cannula perforates what is felt to be a thin membrane. This sensation of perforating a membrane is typical, and there is ample evidence that such is the situation.[28-30]

The term dacryostenosis, then, is a convenient but poor one, since there is no actual narrowing or stricture of the nasolacrimal duct. Congenitally imperforate nasal ostium or nasolacrimal duct would be the proper but somewhat more cumbersome term. I

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Illustration to show positioning technique. Adequate immobilization of the infant is accomplished by swathing. The head is steadied by an assistant who uses a thumb, with gauze for traction, to depress the lower lid until punctum dilatation is performed and the cannula has been introduced.

believe that it describes the condition with greater exactitude than "congenital impatency of the nasolacrimal duct," as suggested by Guerry and Kendig.[6]

Late Probing

In the comparison series of late probings, in 48 youngsters (59 nasolacrimal ducts) between the ages of 6 and 10½ months, it

was necessary to repeat the probing in two youngsters (two nasolacrimal ducts). Over a period of two and one-half years, all of these youngsters were operated on in the hospital under ether anesthesia with a Bowman No. 1 probe. All of these children were on "conservative" treatment for several weeks or months prior to probing. Nearly all of these youngsters were first seen at a few weeks to 2 months of age, and the daily use of drops consisting of boric acid, zinc sulfate, and epinephrine was prescribed. In addition, sulfisoxazole eye drops were prescribed to be used for a one-week interval during any period in which "mattering" or discharge was found by the parents. Most of these youngsters were reexamined at two-month intervals, and an attempt was made to schedule probing as soon after the age of 6 months had been reached as possible. The sulfisoxazole drops were routinely used for one week prior to the probing in all instances. Using this routine, I have never seen an acute dacryocystitis with lacrimal sac distention in these children.

In this older group, it was very interesting that, in nearly every case, firm areas of resistance were met at various levels in the nasolacrimal duct in addition to that at the lower end of the duct. An especially common place was at what was considered to be the junction of the lacrimal sac and the upper end of the nasolacrimal duct. Moreover, in over one-third of the ducts probed in this series a hard gritty resistance was encountered at the lower end of the duct at or near the nasal ostium. Although this could be felt rather than seen, the unmistakable gritty sensation from the tip of the probe left no doubt as to the bony character of the resistance there. After the tip of the Bowman probe had been passed through the nasal ostium in these youngsters, the probe was slightly retracted and then repassed in a slightly different direction two or three times so that all bony spicules would be fractured away from the nasal ostium. It is clear, then, that much greater trauma was involved with these late probings. Irrigation of the punctum was routinely performed as the final step, and since moderate hemorrhage occurred in the majority of cases, a solution of 1:10,000 epinephrine was used as the irrigating solution.

The two patients who required reprobing both had firm, bony resistance at the nasal ostium and were among the oldest patients in this series. In addition they were initially operated on before this maneuver of repeated fracture of the calcified ostia was instituted, but at reoperation this maneuver was performed, with complete recovery postoperatively.

I have never found it necessary in these late probings to conduct any instrumentation through the nose as has been advocated by Guerry and Kendig,[6] Berry,[31] Woodruff,[32] Gunn,[33] and Larsson.[24] However, with late probing it is conceivable, especially in those instances of calcified nasal ostia, that it would be possible to misdirect the probe to a position underlying the nasal mucous membrane and thereby fail to effect a cure.

A further note in regard to the technique is that in both groups the lower punctum was used in probing the nasolacrimal duct, since this route is somewhat easier when one is standing at the head of the patient. Moreover, since it is the lower punctum and canaliculus which normally convey most of the tears to the nasolacrimal duct, it seems wiser to ascertain the patency of these structures rather than to probe through the less important upper punctum. I have never found this route any more difficult or found any resulting injury to the lower punctum and canaliculus. Furthermore, a straight probing instrument is much to be preferred over a curved probe. The lower punctum and canaliculus, lying in the soft tissues of the lid, are easily manipulated without undue trauma so that a straight instrument may be turned to a vertical position and passed through the remainder of the lacrimal drainage system. Since the nasolacrimal duct is essentially a straight tube, it is inconceivable to me how a curved instrument can be properly used.

Comment

The most remarkable difference in the two series from an operative standpoint was the increased degree of obstruction encountered in the older group. It is reasonable to assume that this was the result of continuous and essentially asymptomatic or subclinical inflammation in the duct, which occurred in spite of the use of antibacterial drops. With this postulate, it is understandable that the most dependent portion of the duct, at the nasal ostium, might become the site of calcified obstruction. In no instance in the younger group was there anything more than a soft, membranous resistance which was encountered at the nasal ostium. In addition, scant hemorrhage or the absence of hemorrhage was the rule in this younger group.

In both series, antibacterial eye drops were prescribed to be used for just one week postoperatively and then stopped. All patients were reexamined at one week, between two and three weeks postoperatively, and again at four months postoperatively. The absence of increased pooling of tears in the lacrimal lake and a negative history of epiphora and discharge were considered sufficient evidence that a cure had been obtained. This was uniformly apparent on the first postoperative visit, with the exception of the two above-mentioned youngsters in the late series. In regard to this, I believe that these are much more important signs than the demonstration of a patent passageway by irrigation of the punctum, which is a demonstration only that fluid under a relatively high degree of pressure will traverse the nasolacrimal duct.

Although the older group apparently obtained just as good a functional result as did the younger group, there are several disadvantages to the later probing. Among these are the necessity for hospitalization and general anesthesia, with all of its attendant risks, and the possibility that a more serious ocular infection may occur, secondary to dacryocystitis, during the period of conservative therapy.[34] There is little doubt in my mind that the nasolacrimal duct remains inflamed, causing destruction and cicatricial adhesions between the duct walls during the period of conservative therapy in these older children.

One argument which has been advanced for deferring probing in favor of a trial on conservative treatment is the claim that upward of 50% of all cases of infants with dacryocystitis will clear spontaneously with conservative therapy.[5,6,35-37] Of the patients that I have seen at an early age with dacryocystitis, only three or four have cleared to the point where I felt that probing was unnecessary. In several of the older youngsters that were probed, there was a history of only intermittent epiphora and discharge, but in all instances in this older subgroup definite obstruction was encountered at probing. It is my belief that in many of these cases which are supposed to clear spontaneously on conservative therapy a careful history will reveal the presence of at least intermittent epiphora and/or discharge. Gamble has expressed the same opinion.[36] Moreover, while some of these youngsters may have a patent duct, they certainly may have a duct which is the site of strictures or stenosis so that the slightest further embarassment, such as an upper respiratory infection, may result in obstruction with stasis, further inflammation, and epiphora and/or discharge. It is a disservice to allow these youngsters to go without probing just because of the cessation of discharge and constant epiphora.

Hydrodynamic cure of congenital dacryostenosis has been described.[38] This is accomplished by the exertion of pressure over the lacrimal sac coupled with massage in a downward direction, toward the nasal ostium. This should be performed so that all of the fluid accumulation in the nasolacrimal drainage system is kept ahead of the massaging finger, causing a fluid wedge to impinge upon the nasal ostium. I have attempted this maneuver many times but have never been successful in curing the dacryostenosis. Moreover, I formerly gave careful

instructions on using this maneuver, as a daily procedure, to all parents of the children on conservative treatment. Its uniform lack of success, however, caused me to abandon this. Although it would seem that this procedure should be effective in at least some cases, as I am sure that it has been in other hands, I believe it is probable that I have never encountered a youngster with a sufficient volume of fluid in the lacrimal sac to form an effective hydraulic wedge. Consequently, I have since instructed the parents of the children on conservative therapy to massage the lacrimal sac daily in the opposite direction, toward the eye, and to clean away any consequent discharge immediately before instillation of the eye drops.

This last type of massage is also a routine part of the one-week preoperative treatment in the early probings. As a result, I have never felt that any appreciable amount of infectious or potentially infectious material has been irrigated into the nose and throat of these infants at the time of probing.

In about 20% of the youngsters in the early probing group, the only sign present on initial examination was increased pooling of tears in the lacrimal lake of the affected eye or eyes. Of this subgroup, there was a history of epiphora, which prompted the parents to seek advice, but no history of discharge and no epiphora at examination. Furthermore, no discharge, mucous or otherwise, could be expressed from the lacrimal sac. These youngsters, then, had dacryostenosis, since obstruction at the nasal ostium was encountered at probing but there was at least no demonstrable dacryocystitis and probably absence of dacryocystitis. I believe that this is the ideal time for treatment of these infants, that is, before dacryocystitis has had a chance to develop. Although the dacryocystitis of early infancy has been described as a mucous dacryocystitis, implying the lack of infection, Nelson has conducted bacteriological studies which tend to contradict this,[18] and it is difficult to believe that infection can be avoided for very long in these untreated infants.

Therefore, it is my opinion that, ideally, these youngsters should be treated whenever possible for the dacryostenosis before dacryocystitis has had a chance to develop. Rather than treating dacryocystitis of infancy, then, we should strive to treat dacryostenosis, which is the predisposing cause of the dacryocystitis.

The diagnosis of dacryostenosis without apparent dacryocystitis is established when expression of the lacrimal sac is unproductive of discharge from the punctum and there is the presence of increased pooling of tears in the lacrimal lake and the history of epiphora. Even though epiphora is absent upon examination, I have found that the presence of increased pooling of tears in the lacrimal lake together with the history of epiphora, from intelligent parents, is sufficient evidence that dacryostenosis is present. Moreover, my experience has been that the history of epiphora in a youngster over 10 days of age should always be considered seriously.

With the group of youngsters in the early probing series and since compilation of the two series, I have striven to perform probing as early as possible after the diagnosis of dacryostenosis has been made. The routine of a few days to one week on antibacterial drops, however, has been maintained. As a result, about 30 infants between the ages of 3 and 4½ weeks have been probed, and in all of these the typical obstruction was encountered.

If this is to be considered radical in an infant so young, I would point out that circumcision, whether phimosis or paraphimosis is present or absent, is an accepted procedure in infants only a few days old and while they are still boarders in the prenatal nursery of the hospital, which is considered to be the optimum time. With the syringe-cannula technique, a properly performed probing is, by comparison, an essentially atraumatic procedure. Moreover, it is performed to cure a definite pathological entity.

With the last 15 infants who have been handled in this manner, 3 of whom are included in the series, I have also probed the nasolacrimal duct of the opposite eye, even though the diagnosis of dacryostenosis had not been made in this fellow eye. Nagel [39] reported in 1920 that bilateral dacryostenosis was rare, but the vast majority of reported series have indicated an average of over 20% bilaterality, and this figure has been approximated in my own experience. Of these 15 youngsters, 3 had bilateral probing in the presence of the previous diagnosis of bilateral dacryostenosis. More significant, however, is that four youngsters were found to have dacryostenosis which was previously undiagnosed in the fellow eye. To me, this is ample justification for routinely probing the opposite tear duct. Perhaps, if these youngsters had not been treated until a later date, the bilaterality would have been apparent as evidenced by epiphora and dacryocystitis in the second eye. Perhaps even worse, however, is the possibility that there might have occurred a "spontaneous cure" in these opposite ducts, resulting in only occasional epiphora in the presence of a patent but stenotic nasal ostium. I believe it is probable that when these four nasolacrimal ducts were probed there may have been patency of their nasal ostia with, nevertheless, a relatively broad area of imperforate membrane remaining. The establishment of the fact that there is no remaining vestige of embryonic membrane to predispose to future trouble is easily accomplished by probing. Once the patient has been immobilized and all preliminary preparations have been made, the probing itself literally takes no more than two or three minutes at the most. Therefore, it seems much simpler to probe the opposite nasolacrimal duct at the same time rather than to subject all concerned to the possible necessity of future treatment for the fellow eye.

Once the possible consequences to dacryostenosis, intercurrent infection with scarring, have been explained, I have never had any parent voice objection as to the youth of the patient to be probed. In fact, many of them, having previously heard that probing is often deferred, have expressed gratitude that the condition could be definitively treated so promptly.

Postoperatively, a few of the parents appear to accept the improvement and cessation of epiphora matter-of-factly, but the vast majority have expressed gratitude or delight that the epiphora and/or discharge have ceased.

Conclusions

1. Congenital dacryostenosis is best treated by early probing shortly after the diagnosis has been made. Optimally, this should be before the end of the second month of life and before dacryocystitis has intervened if possible.

2. The syringe-cannula technique, which minimizes instrumentation, is an ideal method for probing in younger infants with congenital dacryostenosis. Properly performed, this method is effective, noninjurious, and much easier than later probing.

3. The apparent spontaneous cures resulting from conservative treatment probably leave, at best, a patent but stenotic nasolacrimal duct, which is more readily subject to the further insults of recurrent obstruction with inflammation and scarring.

4. The presence of increased pooling of tears in the lacrimal lake coupled with a reliable history of epiphora is sufficient evidence to make the diagnosis of congenital dacryostenosis.

5. In view of the frequency of the bilaterality of congenital dacryostenosis (an average of over 20%), it is considered proper routinely to probe the opposite nasolacrimal duct even in the absence of a diagnosis of congenital dacryostenosis in the opposite eye.

Summary

The experiences encountered in series of both late and early probings for congenital dacryostenosis are presented and compared. This comparison reveals further evidence in favor of probing at the earliest possible age

in order that dacryostenosis can be corrected, and, ideally, that it can be done before the intervention of dacryocystitis.

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Aqueous Floaters in the Differential Diagnosis of Papillitis and Papilledema

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The basic difference between papilledema due to increased intracranial pressure (hereafter referred to as papilledema) and papillitis (the intraocular form of optic neuritis) was first described by Paton and Holmes [1] in 1911. Since then there have been various other references to the same subject in the literature.[2-5] The outstanding features which distinguish the two entities are concerned with the type of pain as well as the type of visual impairment. The funduscopic picture as well as the laterality of the findings are also of importance. For purposes of this paper, these well-known points will be reviewed very briefly.

Pain

In optic neuritis the pain is in or behind the eye and increases with movement of or pressure on the globe. It either precedes the visual disturbance or accompanies it. In papilledema the pain is that of a generalized headache usually preceding the appearance of papilledema by a considerable length of time and not related to movement of the eye.

Vision

In optic neuritis there is sudden onset of a marked blurring of vision which reaches its height within a few hours or days. This visual blur is usually easily demonstrated by a cecocentral or paracentral (less frequently, peripheral) nerve fiber bundle defect. With a cecocentral scotoma, the central visual acuity is markedly affected. In papilledema, on the other hand, there are usually some transient episodes of mild blurring of vision, such episodes occurring only after papilledema has been present for a period of time and preceding, by days or weeks, a more intense and serious loss of central vision. However, such loss of central vision is usually of an insidious nature and follows a transient blurring. In cases of papilledema there is an enlargement of the blind spot which gradually encroaches on fixation to cause the above-described transient episodes of blurring of vision. Peripheral field defects may occur as well, but, again, they are much more insidious in onset than are the field defects in optic neuritis. Moreover, the visual field defects in general are not as sharply demarcated as they are in optic neuritis.

Funduscopic Picture

In papillitis, as in papilledema, there may be blurring of the disc margins, filling in of the cup, edema, exudates, and hemorrhages. While the funduscopic pictures may be somewhat different in these two conditions, most observers agree that they are easily confused and certainly not always characteristic enough to rely on entirely for making such an important differential diagnosis.

Laterality

Papillitis may occur bilaterally simultaneously, but it occurs more frequently unilaterally. Papilledema, on the other hand, occurs bilaterally except in the following circumstances. Some basic anatomic differences, as in the vascular supply to the two discs, may cause the papilledema to show up earlier in one disc than the other—perhaps by a few days. Unilateral myopia may also be a cause of later onset of visible

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papilledema. Unilateral optic atrophy, likewise, would be a reason for the nonappearance or delayed appearance of papilledema in one eye, as in the Foster-Kennedy syndrome.

It would seem that, with all the above differential points available, there should be little difficulty in making the differential diagnosis between the two conditions. On the other hand, when other factors are not entirely conclusive the unilateral appearance of papilledema (even if unilateral for only a day or two) may cause a difficult problem in being differentiated from papillitis. Conversely, the simultaneous bilateral occurrence of papillitis, even though not very frequent, may still be a difficult picture to differentiate from papilledema, especially when the rest of the clinical picture is otherwise confusing. Such a differential diagnosis may be even more difficult when central visual acuity (Snellen) is retained, and such occurrence has been demonstrated.[6]

In speaking of papillitis, at least for the purpose of this paper, one should include also those entities which cause an inflammatory reaction of the discs—whether primarily an optic neuritis, or neuroretinitis, or secondary to chorioretinitis or uveitis. Thus, in 1955, Zimmerman [7] pointed out the occurrence of inflammatory cells in the optic nerve head in optic neuritis, papillitis, and neuroretinitis. He further emphasized that the pathologist labels these as papillitis, even though the clinician may not find evidence of a scotoma and therefore labels them as papilledema. Therefore, Zimmerman suggests that not only infections but degenerative, nutritional, toxic, and vascular disorders be considered under the general heading of optic neuritis, owing to the fact that they all show inflammatory cells pathologically. That optic neuritis may occur secondary to uveitis, even anterior uveitis, has been shown by a number of observers.[8-10] It may be that the secondary occurrence of optic neuritis is more frequent with posterior uveitis than with anterior uveitis.

Conversely, in cases of optic neuritis, some inflammatory products are believed to reach the aqueous through the vitreous. This view was expressed by Selinger,[11] who showed a definite elevation of the protein content of the aqueous in patients with papillitis as compared to patients with papilledema. Thus, in patients with papilledema, the protein content of the aqueous remained at less than 0.02%, which is normal, while in patients with papillitis the protein content of the aqueous went up to as high as 0.04% and even up to 0.10%. Selinger arrived at these figures by performing anterior chamber punctures, removing the aqueous, and analyzing it for its protein content chemically—a somewhat difficult if not a risky procedure for routine clinical study.

Aqueous Floaters in Cases of Papillitis

Suspecting that papillitis may cause the appearance of inflammatory cells in the anterior chamber, I have been using the slit-lamp biomicroscope to examine the aqueous in all cases of edema of the disc, whether believed to be due to papillitis or papilledema. In order to make an adequate study of the aqueous, it was found necessary to examine the aqueous with widely dilated pupils before being able to detect or rule out floaters and flare in some cases. The finding of only an occasional brownish floater in an otherwise clear aqueous was not interpreted as evidence of inflammatory reaction, since it is well known that wide dilatation with mydriatics may cause the appearance of an occasional floater even in the absence of an inflammatory process. On the other hand, the finding of a substantial number of floaters in a beam of light across various portions of the aqueous, and especially in the presence of a slight flare or turbidity in the slit beam, may be considered as possible evidence of intraocular inflammation.

The cases of papilledema were not recorded for this paper. Suffice it to say that about two dozen cases of papilledema, all of which later followed a clinical course sub-

stantiating the diagnosis of papilledema, were examined, and in none of them were any abnormal floaters or flare found. This may be in keeping with the observation of Zimmerman,[7] who reported a "noteworthy absence of inflammatory cells" in the histopathological study of papilledema.

In the following four cases, on the other hand, good clinical evidence for an inflammatory lesion seemed to be obtained by the finding of floaters or flare in the aqueous.

Report of Cases

CASE 1.—A 9-year-old white boy was admitted to the Montefiore Hospital on Feb. 16, 1957, with a complaint of headache for the previous four weeks. He vomited on several occasions. He was said to have bilateral papilledema, bilateral sixth nerve palsy, and limitation of upward gaze. Ophthalmological examination revealed that his so-called headache was really confined to the area above his eyes. Vision was 20/30 in the right eye and 20/40 in the left. External examination showed a very mild conjunctival injection of both globes and a suggestion of some periorbital edema. Retropulsion of the globe caused some local pain. Extraocular motility showed some slight inconstant extraocular muscle palsies. The pupils reacted normally. The fundi revealed mild but definite edema of the nerve heads, with loss of all margins and cups, fullness of the retinal veins, but no hemorrhages. The edema did not appear to end immediately around the disc area but seemed to show a rather gradual continuation into the extreme periphery of the retina, which assumed a slightly yellowish dull reflex instead of the shiny shimmering orange reflex normally seen in a 9-year-old child. What was interpreted as being due to retinal edema, reaching as far peripheral from the disc as it did, gave the impression that it reached too far into the periphery for the rather mild amount of papillary involvement if the papillary involvement were due to increased intracranial pressure alone. In other words, even with definite papilledema, when due to increased intracranial pressure, the edema is apt to involve the retina for a limited distance, perhaps as far as 2 or 3 D. D. away, but rarely more, at least in the early stages. In this particular case, the peripheral extent seemed far out of proportion to the small amount of local papillary congestion present as stated above.

Slit-lamp examination revealed numerous floaters in the anterior chambers of both eyes, together with a slight flare. Under dilatation these findings became much more pronounced. Visual fields revealed a normal periphery for 2/330 white in each eye. Central fields disclosed enlarged blind spots with some encroachment on the central field for 1/2000 white in the left eye (Fig. 1).

On the basis of the ocular findings, a diagnosis of an inflammatory disease was suggested. However, because of the lack of findings of specific scotomas and the history of vomiting, a ventriculogram was done and showed a normal ventricular system. Spinal fluid examination revealed normal pressure, clear colorless fluid, and normal protein content. Several days later, the patient developed some tenderness in the anterior thigh muscles.

Because of the bulbar injection and ocular tenderness as well as the periorbital edema, an inflammatory process involving sclera and orbital tissues was considered and also believed to account for the inconstant limitation of ocular motility. Concomitant involvement of the uvea and retina, involvement of the orbital tissue, and the subsequent tenderness over the thigh muscles led to a diagnosis of dermatomyositis, one of the collagen diseases.

Under the effects of systemic steroids, the entire clinical picture subsided in a period of several weeks.

The visual fields here indicated greater encroachment on the 1/2000 field in the left eye than the right. Unfortunately, the field for 0.5/2000 was not determined. It may well be that this isopter may possibly have shown the actual encroachment on fixation to account for the drop of visual acuity to

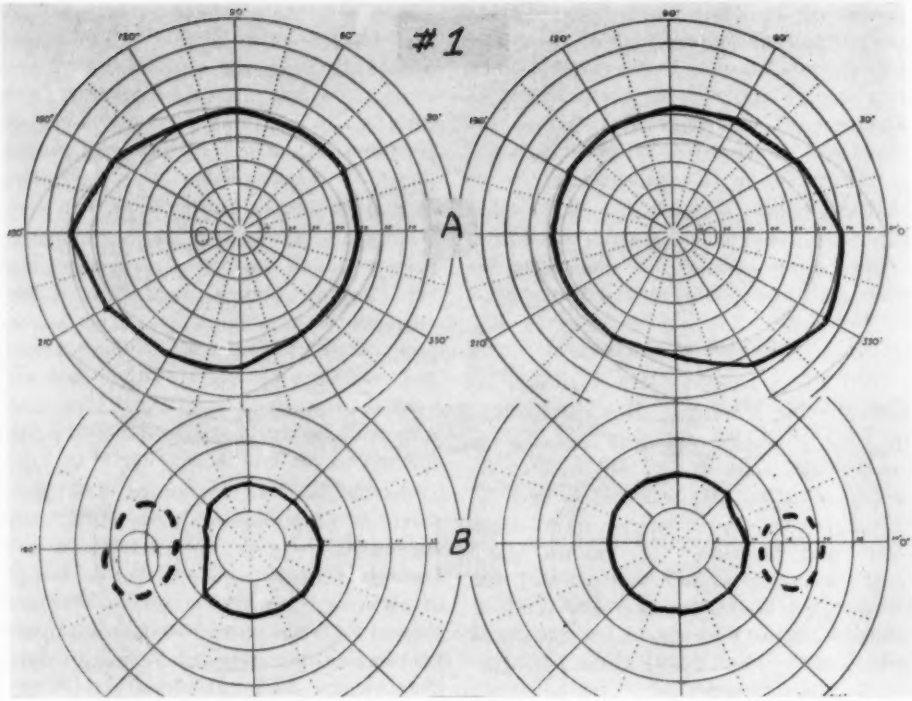

Fig. 1 (Case 1).—Vision in right eye 20/30, left eye 20/40. *A*, peripheral fields for 2/330 white. *B*, central fields for 1/2000 white. Left blind spot for 5/2000 white and right blind spot for 2/2000 white.

20/40 in the left eye and 20/30 in the right. It would seem from a field study such as this that a mild inflammatory reaction involving the choroid and retina may well have been present to account for the diminished vision without the demonstration of an actual discrete scotoma for 1/2000 white. On the other hand, it may be that this type of disc would show, histopathologically, the picture that Zimmerman [7] refers to as papillitis by virtue of the finding of the inflammatory cells histopathologically even though a central or paracentral scotoma is not demonstrated clinically and may lead the ophthalmologist to a clinical diagnosis of papilledema rather than papillitis.

In this case, aside from supporting clinical data, the finding of floaters in the aqueous, as well as the peripheral extent of edema in the retina, helped to make a diagnosis of an inflammatory lesion (papillitis) rather than papilledema.

Case 2.—A 39-year-old man with a history of headache and blurring of vision in the left eye for the previous six weeks was admitted to the Bronx Municipal Hospital Center on Sept. 6, 1957. During these six weeks he had been seen by an ophthalmologist who found bilateral "papilledema" and therefore had referred him to a hospital as a brain tumor suspect. The hospital workup reportedly disclosed some evidence of a brain tumor, but the patient refused further treatment at that institution at that time.

Examination revealed visual acuity of 20/20 in each eye, despite the patient's history of blurring in the left eye. Both discs showed definite edema extending for several disc diameters beyond the margins, with some small hemorrhages immediately around the disc.

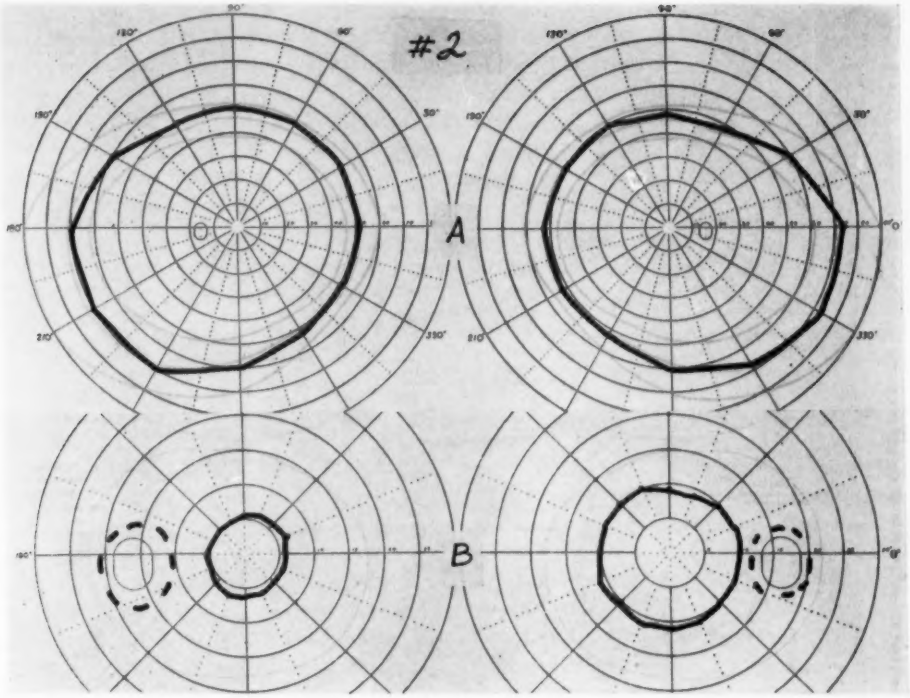

Fig. 2 (Case 2).—Vision 20/20 in each eye. *A*, peripheral fields for 2/330 white. *B*, central fields for 1/2000 white. Blind spots for 5/2000 white.

Slit-lamp biomicroscopy revealed numerous fine floaters together with a faint flare in the anterior chamber of each eye. These floaters and flare were visualized much better after wide dilatation with 10% phenylephrine (Neo-Synephrine).

Spinal tap revealed a pressure of 95 mm. of water, protein of 77 mg., and cell count of 50 white blood cells. The electroencephalogram was normal. Visual fields revealed a normal periphery for 2/330 white but definitely enlarged blind spots for 5/2000 white. The central field for 1/2000 white was contracted in the left eye (Fig. 2).

The subsequent clinical course revealed no other pertinent findings. The use of steroids systemically and locally in the eyes helped to control the uveitis, and eventually the inflammatory process subsided, leaving only some of the usual sequelae of a posterior as well as an anterior uveitis. The clinical evidence indicates that there was some diffuse involvement of the optic discs but no discrete patch of chorioretinitis.

In this case, as in Case 1, the presence of aqueous floaters as well as the peripheral extent of the retinal edema helped to make a diagnosis of an inflammatory lesion.

Case 3.—A 13-year-old white girl was admitted to the Montefiore Hospital on May 30, 1957, complaining of poor vision and pain in the right eye for one week.

Visual acuity was 20/25 in each eye. There was pain and tenderness over the right globe. Funduscopic examination of the right eye revealed that the disc margins were completely blurred, with the greatest part of the edema of the disc being in the upper portion of the disc. There were some hemorrhages around the disc. In the left

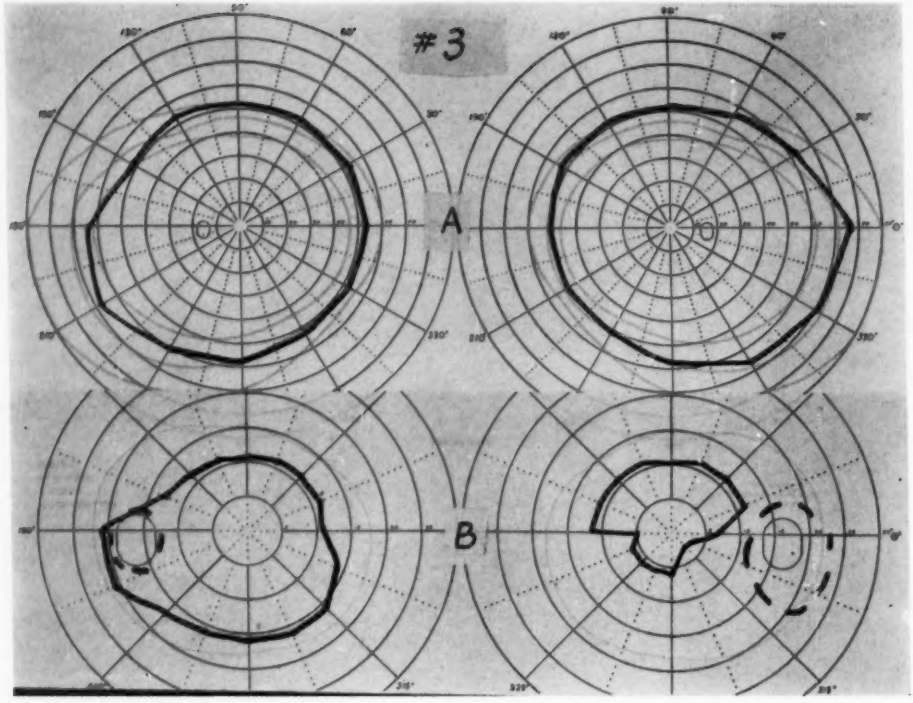

Fig. 3 (Case 3).—Vision 20/25 in each eye. *A*, peripheral fields for 2/330 white. *B*, central fields for 1/2000 white. Left eye shows normal blind spot for 2/2000 white and normal field for 1/2000 white. Right eye shows lower paracentral nerve fiber bundle defect for 1/2000 white and large blind spot for 5/2000 white.

eye, the color of the disc was normal and there were good sharp margins, together with a small cup. Slit-lamp examination revealed many floaters in the anterior chamber of the right eye only. None were present in the aqueous of the left eye.

Because of the retention of normal central visual acuity, ophthalmological consultation was sought to corroborate the diagnosis of papillitis rather than papilledema. Of course, the unilaterality of this picture, together with the local tenderness, was actually good clinical evidence for papillitis. The finding of a lower paracentral nerve fiber bundle defect helped to corroborate the diagnosis, and the preservation of 20/20 vision is well known in cases such as this [6] (Fig. 3).

While the other clinical evidence was convincing enough to the ophthalmologist, nevertheless, the finding of numerous floaters in that eye served as substantial corroborative evidence of the presence of an intraocular inflammatory process, namely, intraocular optic neuritis or papillitis. The subsequent clinical course in this case substantiated the diagnosis of papillitis.

Case 4.—A 27-year-old Negro woman was admitted to Montefiore Hospital in November, 1957, complaining of pain around her eyes together with loss of vision of two weeks' duration. Because of the bilaterality of the disc edema, papilledema had been suspected, and the patient was admitted to the neurological service of the Montefiore Hospital. Ophthalmological consultation was requested, and examination revealed visual acuity of 1/200 in the right eye and 20/400 in the left. The pupils reacted sluggishly. Both fundi showed blur-

ring of the discs, especially the nasal margins. The right disc also showed a small hemorrhage off its nasal border.

Visual fields were severely impaired, and examination, which was limited to confrontation testing with hand movements, revealed a severe loss of the lower field of vision in each eye.

Under the slit lamp, with the pupils dilated, numerous floaters were found in the aqueous of the right eye and fewer, in the left.

With the use of systemic steroids, visual acuity improved rapidly.

Comment

In analyzing the first three cases, it would seem that there was actually enough clinical evidence to point to an inflammatory process in each of them even without the finding of floaters in the anterior chamber. In Case 1, the uveal and retinal picture is believed to be part of the disease entity known as dermatomyositis, one of the collagen diseases recently given a good deal of attention in the ophthalmic literature.[12] In Case 2, no associated systemic disease relating to the neuroretinitis could be found. In both of these cases the observation of a yellowish dulling of the retinal reflex reaching well beyond the disc margins (and out of proportion to the amount of papillary congestion if due to papilledema) is worthy of note and may be considered as clinical evidence of inflammatory involvement of the peripheral retina. In Case 3, while the clinical evidence was convincing enough of papillitis, the preservation of central visual acuity of 20/25 in each eye left the neurosurgeon somewhat concerned with the possibility of this being papilledema due to increased intracranial pressure and showing up in one eye before the other. Actually, the visual field change showing a paracentral nerve fiber bundle defect with preservation of central visual acuity of 20/20 was compatible with acute papillitis. However, the finding of numerous floaters and flare in the aqueous of that eye together with the completely clear aqueous in the other eye served as corroborative evidence of the presence of an inflammatory process, namely, optic neuritis or papillitis in this case.

In Case 4, while the history and other clinical findings were typical enough of bilateral optic neuritis, the aqueous floaters gave additional evidence for an inflammatory process.

While currently accepted criteria for the differential diagnosis of papilledema and papillitis are, in most instances, adequate, it appears to be clinically useful to utilize the two criteria presented here—namely, aqueous floaters and peripheral retinal edema well beyond the disc area—as evidence of papillitis rather than papilledema. In those instances where the peripheral retina is involved, it may well be that the disc is involved merely as a contiguous involvement of the retina. Clinically, one may label this as neuroretinitis. It would also seem reasonable that when there is such diffuse involvement of the disc one may not find a discrete scotoma but rather diffuse mild involvement of the central field, as in Case 1. It may also be that this type of case fits into the pathological picture described by Zimmerman, namely, the type of case which shows inflammatory cells histopathologically and, therefore, is labeled as papillitis by the pathologist but fails to show a discrete scotoma clinically and is therefore labeled as papilledema by the ophthalmologist. For such entities, I would propose the term *diffuse papillitis*, in contrast to the picture in Case 3, where there is a definite dense nerve fiber bundle defect, due undoubtedly to a localized infiltration of the corresponding nerve fiber bundle by a fairly discrete accumulation of inflammatory cells. To differentiate this type of case from the one of diffuse papillitis, one might use the term *focal papillitis*. This term of course, would include the usual type of optic neuritis with a typical nerve fiber bundle defect.

While this report is based on only a few cases, the observations seem reasonable and useful and therefore worth reporting. The existing literature does not seem to mention these criteria as possible diagnostic points for this differential diagnosis.

To say that all cases or even most cases of papillitis will show aqueous floaters would be unwarranted at present. Only time and examination of many more cases will answer this question. On the other hand, it seems reasonable to say that when floaters or flare are found in the aqueous this would be a point for papillitis rather than papilledema.

The importance of differentiating papillitis from papilledema is further emphasized by Wagener,[13] who, in his discussion of the fundus pictures in cases of encephalitis, concludes that adequate estimation of visual acuity and visual fields is essential in such cases. He very properly points out the difficulty in obtaining such estimations in the very young and the sick. It would appear, therefore, that the finding of floaters may well be utilized in such cases to help solve an otherwise difficult problem.

Summary and Conclusions

The presence of aqueous floaters is offered as evidence of a posterior ocular inflammatory process such as papillitis and, therefore, as a diagnostic point for papillitis rather than papilledema. Such papillitis may be due to a focal lesion in the optic nerve or to a diffuse involvement of the disc secondary to choroidal or retinal inflammation.

The extension of retinal edema well out into the periphery, beyond what one would ordinarily see with the amount of disc congestion that would result from increased intracranial pressure, is additional evidence for an inflammatory lesion involving retina as well and may help to diagnose the papillary involvement as papillitis rather than papilledema.

The terms *diffuse papillitis* and *focal papillitis* are offered as simple descriptive terms for the clinicopathologic entities discussed in this paper.

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The Role of the Streptococcus in the Pathogenesis of Anterior Uveitis

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Anterior, or nongranulomatous, uveitis is generally believed to represent an allergic reaction of the delayed bacterial or tuberculin variety. Woods [1] has summarized the evidence for this concept which rests mainly on (1) the experimental production of nongranulomatous uveitis in laboratory animals with various antigens, (2) the clinical evidence that the uvea participates in general systemic hypersensitivity, as in serum sickness, and (3) the absence of any bacteriologic cause, as demonstrated by repeated failures to cultivate organisms from the aqueous during the course of the disease.

Dr. Woods' observations suggest the Streptococcus as the prime etiological antigenic agent in the majority of instances. He bases this view on the following evidence:

First, the evidence of prior infection with the Streptococcus as revealed by the presence of elevated antistreptolysin (ASL) titers in patients with nongranulomatous uveitis. This has been confirmed by Schöne and Steen [2] and by Smith and Ashton.[3] This observation was originally corroborated by Leopold and Dickinson.[4] However, in a recent communication to us, Leopold has questioned the association of elevated ASL titers and uveitis on the basis of additional evidence.[5]

Second, the evidence of a specific hypersensitivity to streptococci as revealed by skin testing. Using stock streptococcal vaccines, Dr. Woods has shown that 80% of patients with nongranulomatous uveitis responded with a specific streptococcal skin hypersensitivity, whereas only 20% of patients with granulomatous uveitis reacted positively.[1]

Third, his observation that patients who demonstrated skin hypersensitivity could be desensitized to the specific bacterial products to which they had reacted.[1] This therapy either terminated the uveitis or diminished the frequency and severity of the attacks, at the same time prolonging remissions between exacerbations.

In this study we were principally concerned with evaluation of the antistreptolysin O (ASLO) titer in anterior uveitis.

There has been only one published report on ASLO titers and uveitis in this country, that by Leopold,[4] and several contradictory reports have been published in the European literature.[2,3,6-8] In view of this paucity of data we performed serial ASLO titer determinations on patients with uveitis and on a control group in order to define more clearly the association between nongranulomatous uveitis and changing ASLO titers.

Methods and Materials

Blood samples were obtained from all new patients on their first visit to the uveitis division of the Bellevue Hospital Eye Clinic and thereafter at intervals of two to four weeks until the disease was quiescent or the ASLO titers remained constant. The patients were questioned for evidence of recent upper respiratory infections. Patients with traumatic or postoperative uveitis or Boeck's sarcoid were eliminated from this study. Simultaneously, blood samples were obtained from other clinic patients unaffected with uveitis, as far as possible cor-

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ANTERIOR:

MALES	21	TOTAL ASLO DETERMINATION	116
FEMALES	15		
TOTAL	36		

POSTERIOR:

MALES	20	TOTAL ASLO DETERMINATION	89
FEMALES	12		
TOTAL	32		

CONTROLS:

MALES	50	TOTAL ASLO DETERMINATION	96
FEMALES	46		
TOTAL	96		

Fig. 1.—Total ASLO determinations in patients with uveitis and in the control group.

relating the control group with the experimental group as to sex and age. The samples were centrifuged within 24 hours, and the ASLO titers were determined by the method described by Todd, which measures the amount of serum required to neutralize two and one-half hemolyzing doses of streptolysin in an indicating system of red blood cells.[9]

A total of 301 ASLO determinations were performed on 68 patients with uveitis. Of these, 116 determinations were on 36 patients with anterior uveitis and 89 were on 32 patients with posterior uveitis. Only random ASLO titers were determined on 96 control subjects (Fig. 1).

Results

For the purpose of this study we accepted a titer of 125 units as the upper limit of normal. Since so-called normal values vary in different laboratories, depending upon the techniques employed and the findings in the control population, it is often difficult to compare results. It has also been observed that there is a marked seasonal incidence of elevated ASLO titers, the peak occurring in February and March. Consequently it was necessary to establish our own controls for this study.

TITER	ANTERIOR	%	POSTERIOR	%	CONTROLS	%
50	62	53	47	53	46	48
62	15	13	12	14	13	14
83	13	11	7	8	13	14
125	13	11	9	10	12	13
	103	86%	75	85%	84	89%
156	6	5	2	2	6	6
208	2	2	4	4	0	0
250	2	2	2	2	3	3
312	2	2	3	3	2	2
416	0	0	1	1	0	0
500	1	1	2	2	1	1
TOTAL	116	100%	89	100%	96	100%

Fig. 2.—Percentage and numerical distribution of ASLO titers in patients with anterior and posterior uveitis and in the control group. Figures in double lines indicate totals for the normal distribution.

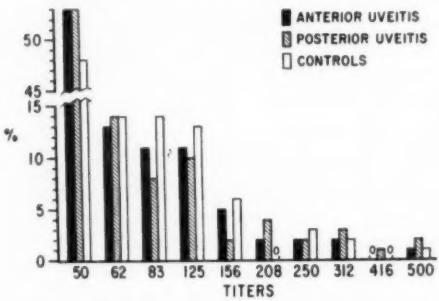

Fig. 3.—Bar graph showing percentage distribution ASLO titers in patients with anterior and posterior uveitis and in a control group.

Our results (Figs. 2 and 3) indicate that there is no appreciable difference in the ASLO titers in the three groups. In the patients with anterior uveitis, serial testing revealed that 86% had titers of 125 units or less; in patients with posterior uveitis, 85%, and in the control group, 89%. Figures 2 and 3 indicate that the distribution of abnormal titers is also comparable in the three groups.

Comment

Our data do not support the concept that there is a correlation between uveitis, either anterior or posterior, and ASLO titers. Consequently, contrary to our previously stated opinion,[10] our data do not establish a causal relationship between anterior uveitis and Streptococcal infection, insofar as this information can be obtained from ASLO titer determinations.

In only five patients in this study was there a suggestive correlation between the course of the disease and an elevated titer which later reverted to normal during the course of serial testing.

However, four of these were patients with posterior uveitis and only one was a patient with anterior uveitis. This is at variance with previous reports that elevated ASLO titers are more commonly found in anterior uveitis.

In one of these patients, Case 1, a 12-year-old Puerto Rican girl, a diagnosis of toxoplasmosis was made on the basis of an acute central choroiditis in the right eye, an old healed central chorioretinal scar in the left eye typical of toxoplasmosis, and a strongly positive Toxoplasma skin test.

On the assumption that her ocular pathology was due to toxoplasmosis, she was treated with pyrimethamine (Daraprim) and sulfadiazine, to which prednisolone was added because of the central nature of her lesion. Three weeks after treatment her vision had returned to 20/30 in the right eye. However, her antistreptolysin O titer was markedly elevated during the acute phase of her disease and gradually returned to normal during the subsequent convalescent course. This finding is shown in Figure 4. It is interesting to speculate that the course of her disease could have been altered by a streptococcal hypersensitivity as well as by a reaction to the toxoplasma organism. It could also indicate that the ASLO titer elevation is of no significance whatsoever and that it was merely an incidental accompanying finding, due to a recent unrelated upper respiratory infection. This points out the difficulty in interpreting positive findings in patients with uveitis.

Another patient (Case 2) with anterior uveitis and an elevated ASLO titer during the course of serial testing gave evidence of a severe upper respiratory infection shortly prior to the onset of uveitis which persisted into the early stages.

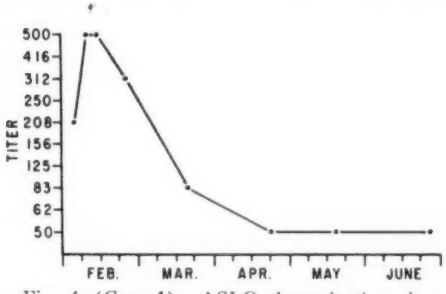

Fig. 4 (Case 1).—ASLO determinations in a patient with presumed ocular toxoplasmosis.

The significance of the ASLO determination should rest upon a changing titer in individual patients and not on a statistical average figure, for the obvious statistical reason that a few high normal titers could distort the average.

Schöne and Steen [2] did report higher ASLO titers in patients with "acute iridocyclitis" than in control subjects. However, it is our opinion that serial ASLO titer determinations on single patients would be more convincing evidence. Smith and Ashton report high individual titers in a small series of patients with anterior uveitis.[3] However, they make no mention of controls, nor do they state whether serial or random determinations were performed.

Contrary evidence has been obtained by other investigators in regard to the antistreptolysin titer and uveitis. Björk [6] was unable to find any elevation of the titer in a series of 54 patients with acute iridocyclitis. He found that his figures were similar to those of the controls even though he accepted 200 units as the upper limit of normal. Vesterdal [7] in Sweden and Stansworth [8] in England state that they could find no correlation between uveitis and antistreptolysin titers.

Our data do not support the thesis that there is an association between antistreptolysin titers and anterior or posterior uveitis. By inference, it seems warranted to take the position that there is no proof of a causal relationship between anterior, nongranulomatous uveitis and the β-hemolytic Streptococcus.

Other evidence advanced to support the thesis that the Streptococcus plays an important role in the pathogenesis of anterior nongranulomatous uveitis involves discussion of the merits of skin testing with streptococcal products and an evaluation of desensitization procedures.

Skin Testing

The diagnosis of bacterial allergy of the uvea based on skin tests may be misleading. Although the skin may be an index of general hypersensitivity, it does not necessarily indicate specific hypersensitivity in any particular organ, such as the eye. Conversely, a negative skin reaction does not necessarily rule out ocular hypersensitivity. It is known that in tuberculosis the skin reaction to tuberculin may be negative yet the patient may have clinical or subclinical tuberculosis of the eye or other tissues. Similarly, a positive reaction to streptococcal skin products does not necessarily implicate the eye as the hypersensitive organ.

Interpretation of skin tests is hazardous because of variables that may be introduced by variations in the biological characteristics of the skin being tested and by the presence of nonspecific ingredients in the test material. For example, the skin of a blonde, a brunette, or the atrophic skin of an older person may react differently to the same antigenic stimulus.[11] Skin sensitivity may be affected by the local concentration of histamine, epinephrine, corticosteroids, and antihistamines.[11]

Misleading skin reactions are not uncommon. In some instances a wheal may follow the intradermal injection of any particulate matter. Irritants employed in the preparation of a product may be responsible for the positive reactions obtained.[11] Thus, in skin testing with heat-killed streptococci the reaction elicited may occasionally be due to the particulate nature of the organism apart from any antigenic specificity and lead to false positive results.

The exact clinical significance of positive skin reactions to streptococcal antigens is subject to varying interpretations. Lawrence[12] has found that positive skin reactions to streptococcal products occurred in 88% of 472 hospital patients selected at random. It is generally accepted that, in the population at large, the incidence of positive reactions to streptococcal products increases with the age of the population. It is noteworthy that Lawrence's figure of 88% in a random population corresponds closely with Woods' figure of 80% positive reactions in his patients with nongranulomatous uveitis.

Furthermore, it would appear to us that if streptococcal allergy is indeed responsible for nongranulomatous uveitis it is difficult to understand its low incidence in young patients suffering from rheumatic heart disease[13] or glomerulonephritis. In both of these diseases a Streptococcus is believed to be the etiologic factor, possibly on an allergic basis. Yet less than 5% of uveitis, moreover, predominantly of the posterior variety, occurs in patients under the age of 16, where rheumatic fever and glomerulonephritis are most common.[3]

Desensitization

Evaluation of the therapeutic effectiveness of desensitization in uveitis is difficult owing to the spontaneous exacerbations and remissions of this capricious disease. Indeed, the great variability in the natural course of the disease makes properly controlled evaluation of any therapeutic measure extremely difficult.

Summary

Our study fails to indicate a correlation between antistreptolysin O (ASLO) titers and either anterior or posterior uveitis. By inference, therefore, it is hazardous to assign causal relationship between anterior, or nongranulomatous, uveitis and the β-hemolytic Streptococcus.

It is concluded that the basis for treating patients with anterior uveitis with intravenous stock streptococcal vaccines is not yet fully established.

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Methods of Inducing Anesthesia and Hypotony for Cataract Surgery

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Methods of inducing profound local anesthesia and hypotony will be presented which improve the safety of cataract surgery.

The retrobulbar injection was described by Pooley [1] in 1914. Elschnig [2,3] (1925) and Izaca [4] (1946) found that retrobulbar anesthesia lowered the intraocular tension. Gifford [5] (1949) demonstrated that the retrobulbar injection of procaine (Novocain) hydrochloride alone caused a fall of intraocular tension to about two-thirds of its former level, which he believed was due to paralysis of the extraocular muscles. There is apparently a base tension in the eye to which is added a pressure from the tonus of the extraocular muscles. A complete block of all action of the muscles lowers the intraocular tension.

I have confirmed this in more than 100 cases. I find that the fall in tension is not uniform but is less in glaucoma and varies with the degree of anesthesia that is achieved.

Hyaluronidase was discovered by Meyer [6] in 1936. The first to describe its use in local anesthesia was Kirby,[7] in 1949. Atkinson [8] was the first to report its use in ocular surgery, in 1949. Hyaluronidase increases the speed of diffusion of the anesthetic in the retrobulbar injection, causing more rapid effects on the nerve fibers, producing profound anesthesia. Paralysis of the extraocular muscles develops, and hypotony then occurs. In normal eyes, the addition of hyaluronidase to the retrobulbar injection causes tension to fall 6 to 9 mm. Hg in 5 to 10 minutes. Snydacker et al.[9] (1954) have shown that the retrobulbar injection of hyaluronidase alone has no effect in lowering intraocular tension. Hyaluronidase apparently lowers tension only when injected with an anesthetic.

The addition of epinephrine (adrenalin) to the retrobulbar injection lowers tension in the eye by a vascular effect. It constricts the arteries entering the eyeball and does not interfere with the outflow in the veins. There may also be a reduction of aqueous secretion due to the constriction of the vessels supplying the ciliary body. The vascular constriction of epinephrine also delays the absorption of the anesthetic solution.

Thomassen's [10] review reported that Pagenstecher, in 1878, found a lowering of tension with massage of the eye; Malakoff, in 1893, was the first to measure that fall with a tonometer, and Schiøtz, in 1908, first noted that the tension fell when a tonometer was kept on the eye.

A few moments of slight pressure on the globe to diffuse the anesthetic material in the lid and about the eye was advised by Atkinson [11] in 1934. Chandler [12,13] has been applying finger pressure over the closed eye after the retrobulbar injection of anesthetic solution since 1951. Thorpe [14] found that pressure on the eyeball after the retrobulbar injection prevented retrobulbar hemorrhage, and he has been practicing it for many years.

Kirsch and Steinman [15] (1955) have published excellent studies showing the great advantages of lowering intraocular tension by finger pressure. They use it after the

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retrobulbar injection and advise five minutes of pressure.

The effects of pressure on the eye will vary with the amount used. Grant [16] concluded that, with the pressures employed in tonography, the major effect was the expression of aqueous and a minor effect was the distention of the sclera.

With increasing pressure applied with the fingers, the veins, later capillaries, and finally the arteries are occluded. Some of these results can be seen ophthalmoscopically as pressure is applied against the sclera with a dynamometer.

How the eye will be affected will vary with the amount of pressure and the period of time it is applied. A danger point may be reached when the capillary supply to the ganglion cells of the retina is shut off for a long enough period. It seems to be tolerated for at least a few minutes. Givner and Jaffe [17] exerted pressure against the eye that shut off the retinal circulation for 20 minutes. In the rabbit this caused retinal hemorrhage, while in the monkey only hyperemia of the disc followed. No permanent occlusion of the vessels occurred.

Recovery of the circulation from the few minutes of pressure I employ is rapid and appears to be only a matter of seconds. I have found that the recovery of normal tension usually requires between 15 and 30 minutes after finger pressure has lowered the tension to 12 mm. (Schiøtz).

The experience with pressure on the eyeball before cataract surgery is not yet extensive, but Chandler, Thorpe, and Kirsch have had many hundreds of cases. I have had about 200 without any complication I can ascribe to it, and none has been reported in the literature. So, apparently the eye can tolerate these pressures without serious effects.

A question is whether this pressure should be regulated or whether each surgeon should just use his own fingers, whatever that degree of pressure might be. One series was tested with a measured amount of pressure applied with a dynamometer similar to the Blaxter [18] test. Careful regulation was not found to be essential. Firm finger pressure on the closed lids or over gauze with some massage is all that is necessary. The interruption of the pressure once a minute for five seconds adds additional safety. The total period of three minutes that I use is well within the tolerance of the eye. Kirsch found five minutes of pressure good in his hands. As each person's hand must vary in its pressure, it is difficult to transfer exact advice. However, there is one simple criterion I strongly urge, and that is to check the tension at the operating table with a tonometer. Pressure is used till the intraocular tension falls to a low level, that is, below 12 mm. (Schiøtz). This can easily be achieved in three minutes of pressure. If the tension is higher, pressure is continued till the tension falls to the desired level. The important criterion is not time but the effect. The one effect we can easily measure is the intraocular tension. So, one should learn to use that pressure which in three minutes lowers the tension to a level of 12 mm. or less in most cases.

Two major effects of pressure on the eye can be demonstrated. One is a diffusion of the anesthetic solution, which I consider the most important effect. The other is a reduction of intraocular tension.

Pressure on the eye increases the rate of diffusion of the anesthetic solution so that a more profound level of anesthesia is reached sooner. This is similar to the action of hyaluronidase. The pressure causes the lids and conjunctiva to flatten out, and the eye becomes motionless.

Pressure on the eyeball also expresses some of the aqueous and for a brief period some of the blood in the eye, which causes a greater lowering of intraocular tension. With lower tension, there is lower vitreous pressure. The lens and vitreous sink back into the eye after the incision, while the lid and ocular muscles are powerless to expel them, and so there are fewer cases of vitreous loss. The hypotony is an advantage in that a soft eye requires more

pressure to expel its contents than a tense one.

The question arises whether to use hyaluronidase alone or to apply external pressure on the eye. With hyaluronidase the intraocular tension falls and the anesthetic effects are good, but not to the degree usually achieved with pressure on the eye. If I were to choose one of them, it would be pressure on the eye. However, I have found it best to use both, so that they supplement each other's action.

Another method of inducing hypotony is by administering acetazolamide (Diamox). This lowers intraocular tension, which is extremely important in operating on an eye with high tension in acute glaucoma. I have not found it valuable in cataract surgery in an eye that from the beginning has normal tension. Apparently the lowering of tension is not as important for safe cataract surgery as is profound anesthesia.

These methods which improve the depth of anesthesia and lower intraocular tension have one very serious drawback. The duration of anesthesia is diminished. Scheie et al.[19] showed in rabbit eyes that a retrobulbar injection of procaine hydrochloride lasted 61 minutes, while with hyaluronidase added it lasted only 37 minutes.

Hyaluronidase decreases the duration of anesthesia by approximately 30%, and pressure on the lids acts in a similar way to shorten the period of anesthesia. It seems to follow that, if the anesthetic material is more quickly diffused, it is more effective for a briefer period, as it is more quickly absorbed.

This shorter duration has no effect if the operation is completed within 20 minutes to ½ hour after the retrobulbar injection. But who is sure how long any operation will last? Modern cataract surgery with the dissection of flaps and cornea-sclera sutures has great advantages but is time-consuming. The risk starts at 20 minutes and increases after ½ hour, when the eyeball and lids can move.

So, it is necessary to find ways of prolonging the duration of profound anesthesia. The addition of epinephrine to the anesthetic solution helps to extend the duration of anesthesia about 10% to 20%. It constricts the blood supply, and so the absorption of the anesthetic is prolonged.

Lidocaine (Xylocaine) has been advocated as a much longer lasting anesthetic than procaine. The claims of the early reports have not been fully substantiated. Some reports and my own experience show only a slightly longer action. Scheie et al.[19] reported a shorter duration.

Tetracaine (Pontocaine) hydrochloride has a far longer duration of anesthesia than procaine or lidocaine. Scheie et al.[19] reported that a retrobulbar injection of 0.1% tetracaine had its effect for 82 minutes, in comparison with 62 minutes for 2% procaine and 45 minutes for 1% lidocaine. The addition of hyaluronidase cut the action of the tetracaine to 75 minutes, that of lidocaine to 43 minutes, and that of procaine to 37 minutes.

Tetracaine has had limited use for injection because of the claim that it is too toxic. According to Moore (1953),[20] it is six to seven times as toxic as Novocain. However, it is effective in a concentration one-tenth that of procaine, and so to achieve the same effect it is used in amounts that are about the same as or slightly less toxic than procaine. Tetracaine, according to Moore, has another advantage. Procaine causes vasodilatation, and so epinephrine is needed to counteract it. Tetracaine causes little if any vasodilatation. Moore claims a duration of anesthesia of three to four times that of procaine. Scheie only found a duration of about one-half longer. My impression is that the duration is between 50% and 100% longer than procaine.

For local injection 0.1% tetracaine is advised. In order to get the advantages of the more rapid onset of action of procaine and lidocaine, I have been using a combination of procaine 1% and tetracaine 0.075%. A similar mixture has been used also with

lidocaine 1% and tetracaine 0.075%. To this is added epinephrine (1:50,000) and hyaluronidase, 3 turbidity units per cubic centimeter.

A lid block injection is given, followed by a retrobulbar injection of about 2 cc. of this mixture, as well as a subconjunctival injection, a superior rectus injection, and usually injection for the other ocular muscles. Finger pressure is applied for three minutes, with interruptions every minute for five seconds. Tension is then taken with a Schiøtz tonometer. If the tension is 12 mm. or less, the operation proceeds. If it is higher, pressure is continued till the desired level is attained.

These combinations for the injection have the advantage of allowing profound anesthesia to develop rapidly and to last longer. There is considerable variation in the duration of profound anesthesia with all these drugs, which depends on local tissue and vascular differences as well as with the site of the injection, the preoperative sedation, and the anxiety state of the patient.

In three cases, after the injection and pressure over the closed lids for three minutes, the intraocular tension rose to high levels. This was most unexpected but proved beyond a doubt the importance of determining the tension before proceeding with the operation.

One was the case of a woman who had suffered an acute attack of glaucoma in the other eye five years earlier. She had an acute attack of glaucoma on the table in the eye we had planned to operate on. Pressure and massage were continued, but the tension did not fall. However, the eye was immobile and fully anesthetized. An ab externo incision was carefully made. Iridectomy and cataract extraction followed, with a good recovery.

In the second case, after the retrobulbar injection and pressure for three minutes, the tension was 60 mm. (Schiøtz). Pressure was continued for five minutes longer, till the tension fell to 18 mm. Operation was uneventful.

The third case was a diabetic woman 72 years of age who had a small degree of proptosis following the retrobulbar injection, apparently due to retrobulbar hemorrhage. Intraocular tension rose to more than 60 mm. Pressure with massage was continued for 15 minutes, till the pressure had dropped to 15 mm. Iridectomy and cataract extraction were then performed without difficulty.

A big defect in intraocular surgery is that it is often performed with only partial anesthesia. There is movement of the eyeball and lids. The patient is told to stay still or told to look this way or that way. They should not have the power to move. It is useless to speak of a poor patient. I think it is inadequate anesthesia that causes much of the trouble at operation for which the patient is blamed.

Conditions at the operating table should approach those of operating on a cadaver. I have dissected many dead eyes and have never lost vitreous. The vitreous generates no pressure of its own. It is best when the surgeon exerts the pressure to remove the lens from the eye. The expulsion of the lens and vitreous by a patient requires energy to push them out. This is furnished by muscle contraction, of either the extraocular or the lid musculature. With poor anesthesia, there is often positive pressure exerted on the eye which causes the wound to gape, the iris to prolapse, and the vitreous and lens to be expelled.

With proper anesthesia, the patient should have almost a total unawareness of the proceeding and an inability to react to it.

However this is achieved, cataract surgery is best performed when the eye is soft, the anesthesia is complete with all sensation absent, and all motion of the lids and extraocular muscles is abolished during the entire procedure. Then the surgeon has perfect control of the situation.

Summary

Methods are suggested that make cataract surgery safer. Rapid diffusion of the anes-

thetic solution can be achieved by finger pressure on the closed eye and the addition of hyaluronidase to the anesthetic solution. The most important effect is the profound and extensive anesthesia that paralyzes the muscles attached to the eye and lids. The paralyzed eye will not push out its contents.

These measures also cause hypotony, which adds security in that a soft eye will require more pressure to expel its contents. It is strongly urged to use a tonometer routinely before starting the incision into the globe, as this furnishes a valuable guide.

Rapid induction causes rapid absorption and a shorter duration of anesthesia. This can be extended by adding tetracaine (Pontocaine) hydrochloride and epinephrine (adrenalin) to the anesthetic solution.

1749 Grand Concourse (53).

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Orbital Fractures

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Fractures about the orbit frequently involve orbital structures, and the patient many times presents himself first to the ophthalmologist, or the latter is called in consultation in the management of the patient. Presented here are the diagnostic features of orbital fractures with some various methods of treatment.

Trauma to the face is extremely common in auto accidents, fist fights, athletic injuries, and industrial and home accidents. The broken nose is the commonest of facial fractures, followed by fractures of the zygoma and mandible, although some surveys reverse the order of the latter two.[1,2] There are three rules of thumb which should be kept in mind. Multiple facial fractures are the rule rather than the exception; around one-half are associated with major bodily injuries elsewhere, and at least one-fourth are associated with concomitant head injury.[3]

The "black eye" is the usual presenting picture of orbital trauma, and a fracture should always be suspected. The patient may complain of numbness and swelling around the eye, nosebleed, diplopia, and sometimes difficulty in moving the jaws. Examination reveals the presence of edema, ecchymosis, and asymmetry of the face, especially of the lids and cheek. Palpation of the orbital rim shows point tenderness and at times the classic "step-off" of the depressed inferior rim of the orbit. Air in the lids may be felt, and the presence of anesthesia in the various cutaneous nerve distributions can be tested.

The ocular examination is extremely important from the medical legal standpoint, as well as for the establishment of the functional integrity of the eye. The visual acuity must be obtained, and an ophthalmoscopic examination should be done soon after injury. Examination of the ocular motility gives important information which contributes to the proper management of the case. The function of the vertically acting muscles should be particularly evaluated.

Examination may reveal some displacement or movement of the body of the zygoma or maxilla, along with concomitant tenderness. A hollow percussion sound of the teeth is indicative of a maxillary fracture. The patient's ability to open and close his mouth should be tested.

The roentgenographic examination is not only invaluable for proper diagnosis but indispensable in the determination of the proper management of the fracture. It is universally agreed that the Waters nose-chin position gives an excellent view of the details of the floor of the orbit, the zygoma, the temporal arches, and the antra, while the Caldwell nose-forehead position gives an undistorted view of the orbital margins and the frontal and ethmoid sinuses. Routine posterior-anterior and lateral views of the skull are of little value in the evaluation of facial fractures. Stereoscopic Waters and Caldwell views are most helpful in that they

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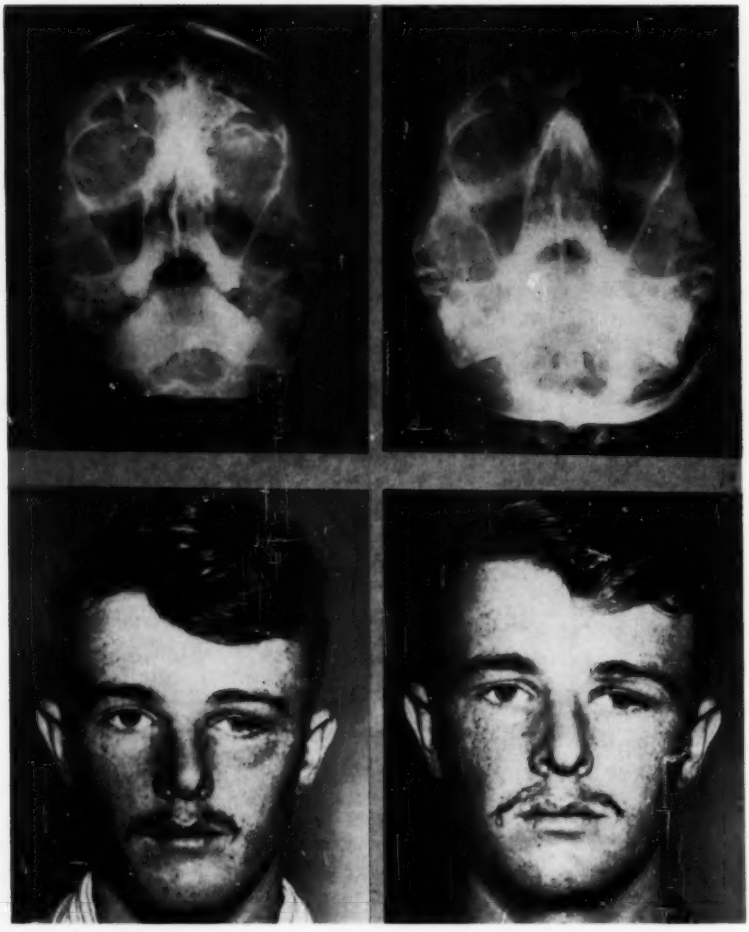


Fig. 1 (Case 1).—Fracture of the left frontal bone with a left pseudoptosis. Pre- and postoperative appearance with x-rays. Open reduction and interosseous wiring.

permit the fullest evaluation of the anatomical damage and the direction and extent of displacement of the various parts. For further details of the zygomatic arch, the submentovertex view is most satisfactory. Laminography may be a valuable adjunct in evaluating the details of some complicated fracture problems.

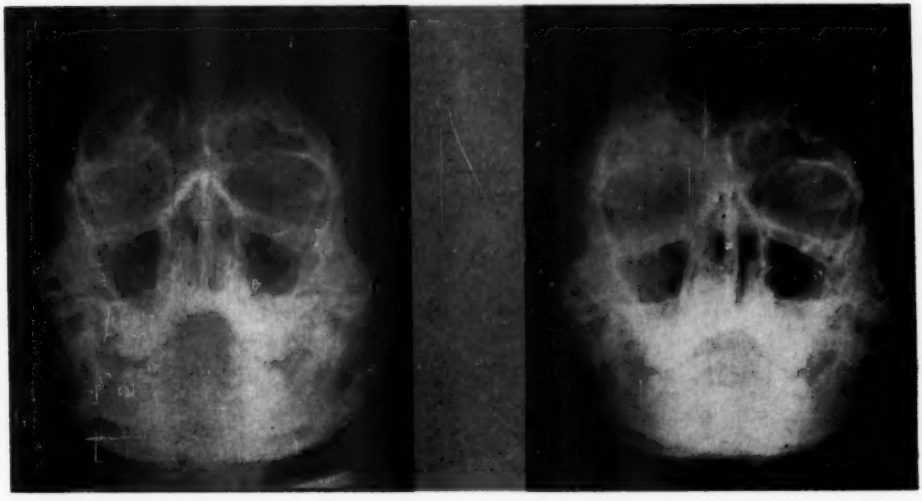
Regional Classification

Orbital fractures can be classified according to their regional involvement as superior, lateral, inferior, or medial.

1. Superior orbital or frontal bone fractures involve the orbital rim, roof, and frontal sinus (Cases 1 and 2). Neurosurgical problems may overshadow the orbital problem because of a fracture involving the anterior fossa with cerebrospinal rhinorrhea, concomitant brain damage, and the possibility of meningitis. Frontal bone involvement is indicated by palpable deformities of the superior orbital rim, supraorbital nerve anesthesia, ptosis, superior rectus weakness, and fracture of the trochlea with superior oblique weakness, as well as orbital hemor-

Fig. 2 (Case 2).—Fracture of the right frontal bone with depression of the brow region and inability to elevate the right eye. Pre- and postoperative clinical appearance.

Fig. 3 (Case 2).—Pre- and postoperative x-rays. Open reduction and interosseous wiring.



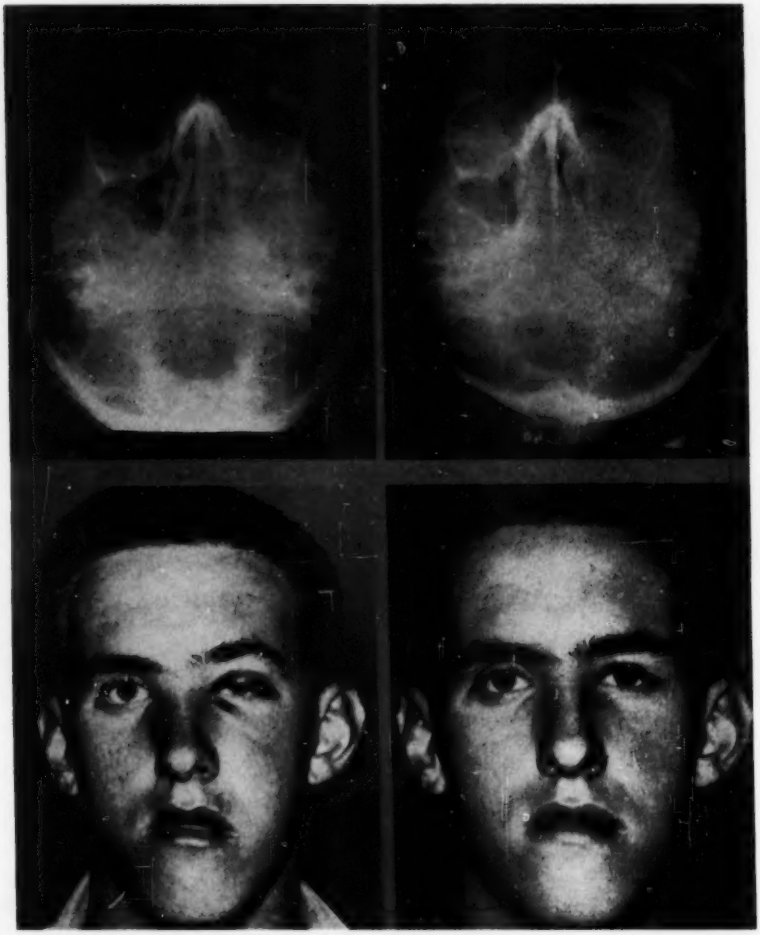


Fig. 4 (Case 3).—Fracture of the left zygoma with separation and displacement of the zygomaticofrontal suture; a left pseudoptosis is present. Pre- and postoperative appearance with x-rays. Open reduction and interosseous wiring.

rhage, emphysema, and infection. Posterior involvement of the orbital roof may produce injury to the optic nerve at the foramen or the orbital apex syndrome.

2. Lateral orbital fractures primarily concern the separation of the zygomaticofrontal suture line, depression of the zygomatic arch and separation at the articulation of the zygoma with the greater wing of the sphenoid (Cases 3, 4, and 5). When the facial edema subsides, the malar eminence is flat. Since the lateral canthal ligament attaches just below and behind the zygomaticofrontal suture, the lateral canthus is displaced downward and backward, producing pseudoptosis and vertical diplopia. A depressed zygomatic arch may impinge upon the coronoid process of the mandible, producing restricted and painful jaw movements. With either of these fractures, lateral gaze diplopia may be present owing to contusion of, or hemorrhage into, the lateral rectus muscle. All of the symptoms and signs of lateral orbital fractures may be masked by edema of the lids with ecchymosis or by concussion damage to the globe

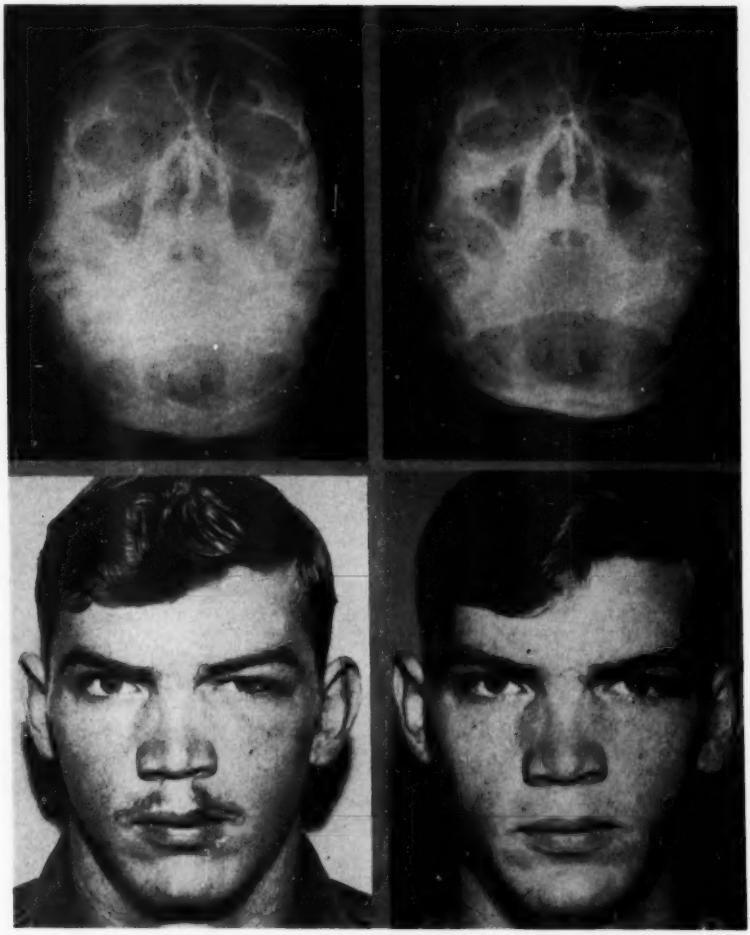


Fig. 5 (Case 4).—Fracture of the left zygoma with separation and displacement of the zygomaticofrontal suture. Pre- and postoperative appearance with x-rays. Open reduction and interosseous wiring.

with reduction in visual acuity. Zygomaticosphenoidal separation damages the inferior orbital fissure, with resulting orbital hemorrhage and proptosis of the globe.

3. Inferior orbital fractures involve primarily the zygomaticomaxillary suture line with concomitant injury to the infraorbital nerve as it emerges through its foramen (Cases 6 and 7). Since the body of the zygoma is solid, it is rarely fractured. Its weaker supports and articulations, however, are vulnerable, and the body is displaced downward and inward through the anterolateral wall of the antrum. A separation or fracture in the vicinity of the infraorbital foramen produces anesthesia of the cheek, the ala of the nose, and the lateral lip. There is local tenderness to palpation of the infraorbital rim with a loss of continuity, and the "step-off" deformity is present. Comminution of the floor of the orbit allows the orbital contents to prolapse into the antrum, producing enophthalmos, downward displacement of the globe, and diplopia. A fracture and displacement of the infraorbital rim may also produce diplopia by dam-

Fig. 6 (Case 5).—Fracture of the left zygoma showing restricted jaw function. Pre- and postoperative clinical appearance.

age to the inferior oblique muscle itself, its origin, or attachments to the inferior rectus and Lockwood's ligament. Since the antrum is always involved, there are tears in the mucoperiosteum, producing hemoantrum with antral cloudiness by x-ray, and perhaps epistaxis.

In fractures of the zygoma, its four major articulations to the frontal, temporal, maxillary, and sphenoid bones are always involved, but one or two are more severely displaced than the others, depending on the angle of force from the trauma. Thus, it is convenient to state that lateral orbital fractures involve primarily the zygomatic arch and the zygomaticofrontal suture, while inferior fractures involve the zygomaticomaxillary suture and the floor of the orbit.

4. Medial orbital, nasoethmoidal, or nasomaxillary fractures occur fairly commonly (Case 8). The fractured ethmoid is easily produced by concussion because of its paper-thinness and results in emphysema of the lids, conjunctiva, and orbit. The major complications in medial orbital fractures are orbital cellulitis, enophthalmos, damage to the lacrimal duct system, damage to the

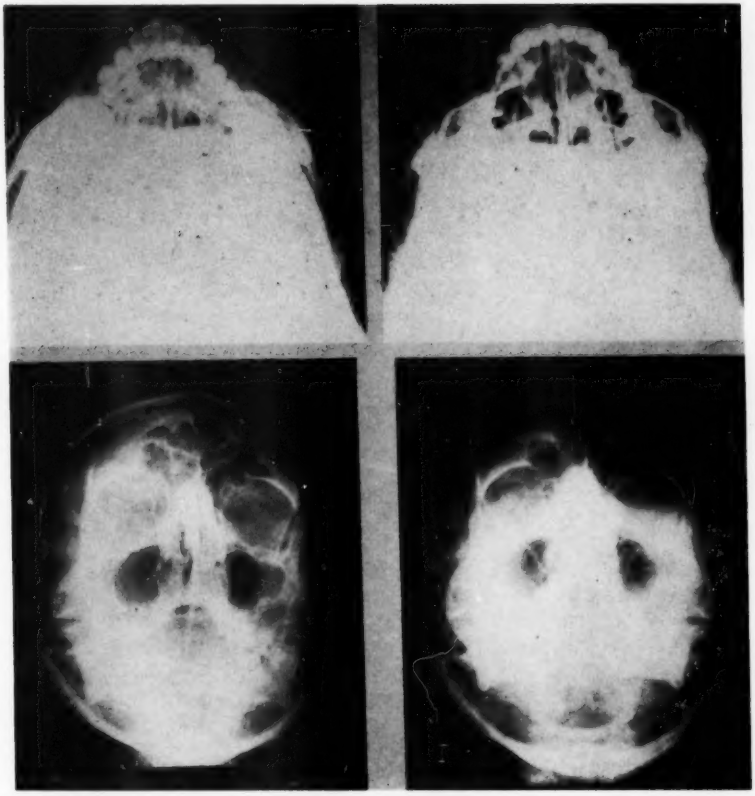


Fig. 7 (Case 5).—Fracture of the left zygoma with separation of the zygomaticofrontal suture and depression of the left zygomatic arch. Pre- and postoperative x-rays. Open reduction and interosseous wiring with the Gillies approach for elevation of the zygomatic arch.

medial rectus muscle, and a traumatic epicanthus.

Treatment

The goals in the proper management of facial injuries are the following: (1) the replacement of bony parts to maintain the symmetry of the facial contour, (2) the maintenance of vision and ocular motility without diplopia, (3) the maintenance of function of the jaws and restoration of occlusion of the teeth, (4) the diminution of facial scars, and (5) the prevention of psychic distress secondary to functional and cosmetic defects.

In the management of the individual patient, the neurosurgical, general, or plastic surgical problems and the concomitant orthopedic problems must be fully evaluated first (Case 9). The management of the individual case varies with the experience and preferences of the individual surgeon. In many cases it involves teamwork, i. e., close cooperation between the ophthalmologist, the rhinologist, the oral surgeon, the plastic surgeon, and the neurosurgeon.

The definitive management of facial fractures can be delayed, if necessary, for about two weeks, since fibrocalcification does not occur until 12 to 21 days after injury.[4] An exception is a mandibular fracture where increase in soft tissue damage necessitates early surgery.[5] Beyond six weeks after injury, the usual closed methods of reduction are impossible, and beyond three months, even open reductions are unsatisfactory.

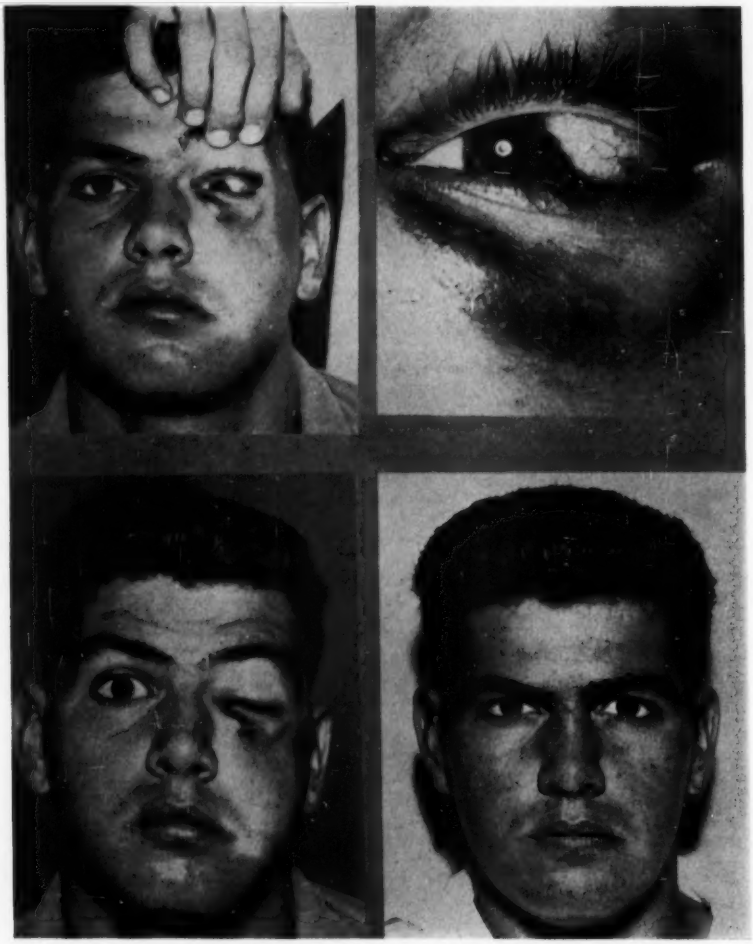


Fig. 8 (Case 6).—Fracture of the left zygoma with emphysema of the lids and conjunctiva. Clinical appearance before and after conservative treatment.

after this latter period of time, only extensive plastic surgical procedures can be used to correct the functional and cosmetic defects.[6]

Improper or delayed management of orbital fractures may lead to a marked facial deformity (Case 10), with associated psychic problems, persistent diplopia, enophthalmos, mandibular locking, and malocclusion of the teeth.

The supportive therapy of all cases includes the use of tetanus toxoid, prophylactic chemotherapy, nasal shrinkage, the avoidance of blowing the nose, and the usual means to encourage the subsidence of edema and ecchymosis of the lids and face. These measures may be employed as the only treatment where minor displacement does not produce deformity or interfere with function (Case 6).

The surgical management of orbital fractures utilizes open and closed methods. With frontal bone fractures, uncomplicated by neurosurgical problems, the restoration of the continuity of the rim and roof of the orbit is usually best accomplished by open

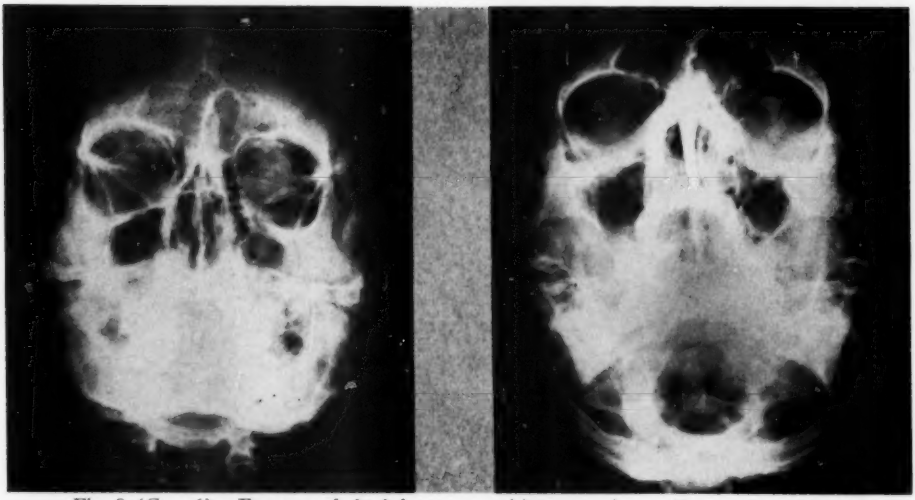


Fig. 9 (Case 6).—Fracture of the left zygoma with zygomaticomaxillary suture separation but with minimal displacement. X-rays before and after conservative treatment.

Fig. 10 (Case 7).—Fracture of the right zygoma with an underaction of the right inferior oblique muscle. Pre- and postoperative clinical appearance.

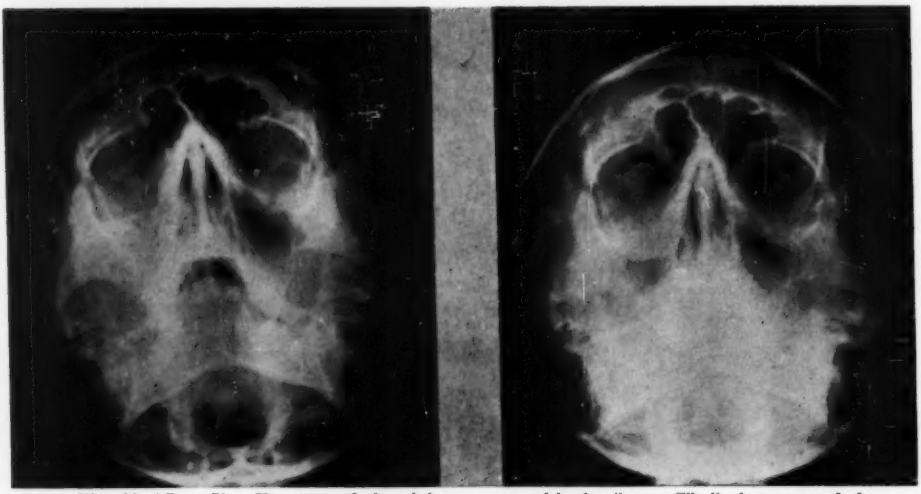


Fig. 11 (Case 7).—Fracture of the right zygoma with the "step-off" displacement of the zygomaticomaxillary suture. X-rays before and after a Caldwell-Luc operation.

Fig. 12 (Case 8).—Nasomaxillary fracture on the right with the nasal bones displaced to the right and with displacement of the medial orbital rim. Caldwell-Luc operation and nasal bone reduction. Clinical appearance after operation with an exotropia, and then three months later after alternate occlusion with restoration of the right medial rectus function.

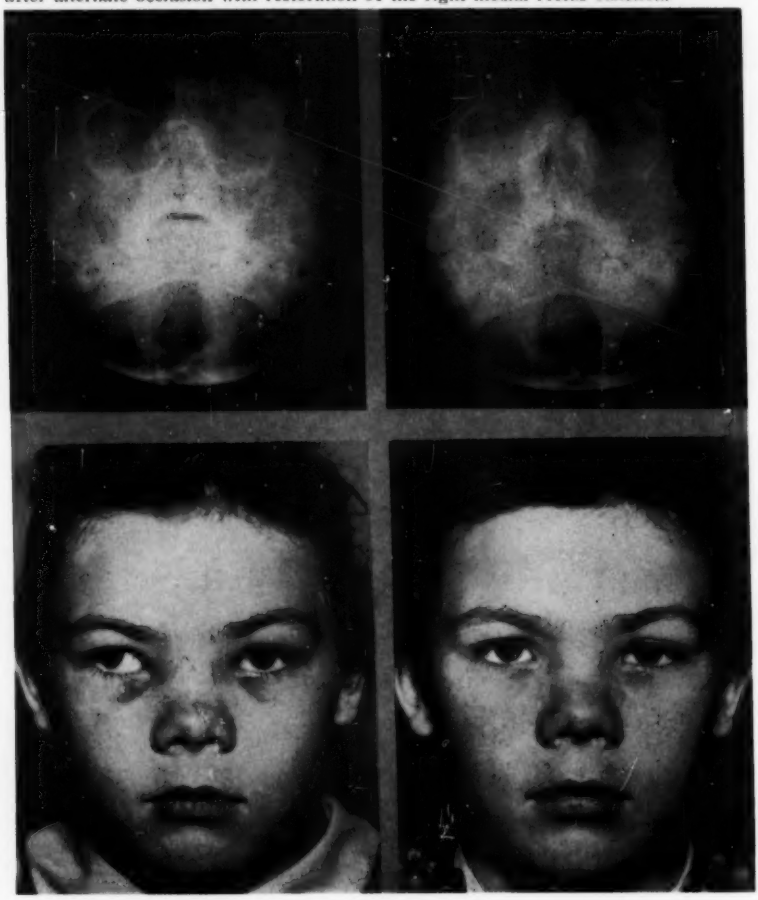
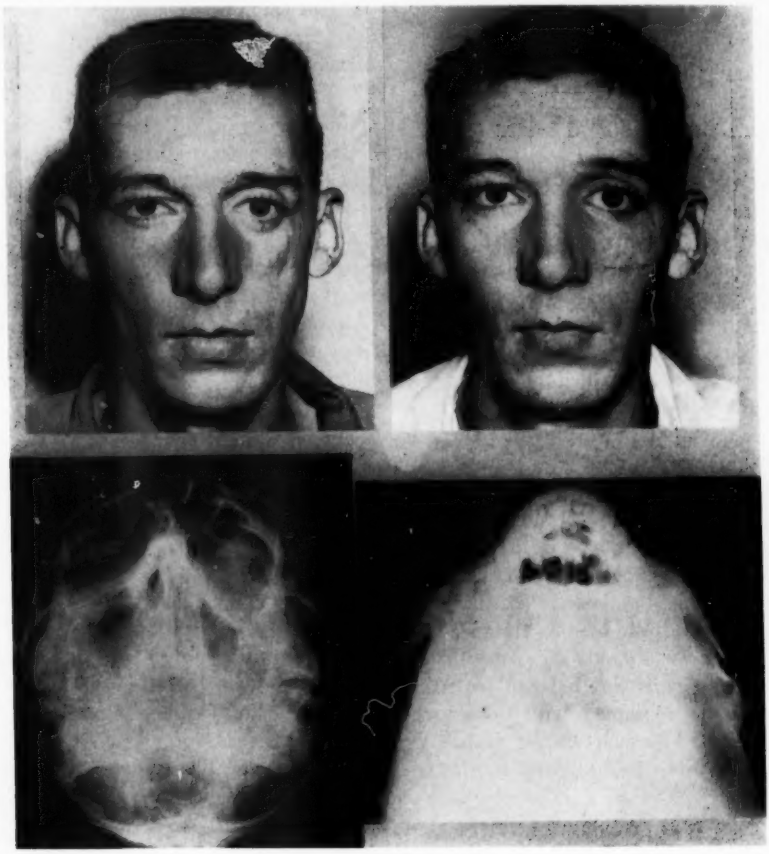


Fig. 13 (Case 9).—Fracture of the left zygoma with marked displacement of the entire body of the zygoma, associated injury to O. S. necessitating enucleation. Concomitant fractures of both lower extremities, pelvis, and skull with fat emboli occurring.

Fig. 14 (Case 10).—Old fracture of the left zygoma with left facial deformity; elongated orbit and depressed zygomatic arch by x-ray. Top right, postoperative appearance after use of an acrylic implant to rebuild the malar eminence.



reduction, debridement, and interosseous wiring (Cases 1 and 2).

For zygomatic fractures, there are numerous techniques.[7-10] The two most widely used closed methods of reduction for simple and uncomplicated fractures are the Gillies approach, via the temporal route, for reduction of the depressed zygomatic arch,[11] and the Kean, or intraoral, approach, for elevation of the body of the zygoma.

These classic closed methods of reduction are used because they create less tissue reaction, are not usually associated with surgical shock, and can be done under local anesthesia. The main deficiency of these methods of closed reduction is the lack of a permanent means of fixation; thus, redisplacement of the fragments can occur due to either pull of the facial muscles or subsequent minor trauma. Also, these temporal and oral closed methods of reduction may incarcerate tissue between the fragments, thus preventing union.

For depressed fractures of the inferior rim of the orbit with comminution of the floor, the Caldwell-Luc procedure (Cases 7 and 8) may be indicated.[1,12] The maintenance of the floor of the orbit through the intra-antral approach is achieved by many varying devices, such as packing, the water balloon, and the jackscrew.[13] In the "blow-out," or internal orbital, type of fracture involving the floor, with herniation of orbital fat into the antrum, elevation of the orbital contents must be maintained. There are advocates for the immediate use of a bone graft [14] or tantalum mesh [15] for this purpose.

When there is a marked separation or depression of fragments, particularly the zygomaticofrontal (Cases 3 and 4) and zygomaticomaxillary sutures, open reduction with elevation [16] and alignment by direct interosseous wiring is indicated.[17-20] It is only with the visualization of the fracture site and its alignment directly by wire that a satisfactory point of fixation can be maintained. Wiring combined with other procedures (Case 5), such as the Gillies or Caldwell-Luc, may be indicated in the individual case.[21,22]

Conclusions

1. Every patient with a "black eye" should be suspected of having a fracture of the orbit. Multiple injuries elsewhere in the body, as well as other injuries of the face, are the rule and not the exception.

2. The clinical examination of the suspected orbital fracture should include the testing of visual acuity and ocular motility, along with the testing of the sensitivity of the cutaneous nerves about the orbit, palpation of the orbital rim, and the evaluation of mandibular function.

3. Stereoscopic Waters and/or stereoscopic Caldwell x-ray views are best for proper evaluation of the injury and as a guide to the institution of treatment.

4. Prophylactic chemotherapy, nasal shrinkage, and tetanus prevention are important therapeutic adjuncts in every case of orbital fracture. These measures may be all that are required in minor or undisplaced fracture cases.

5. In simple fractures of the orbital rim, without major displacement, the classic closed methods of manipulation and reduction are excellent and relatively easy to perform.

6. Open reduction with direct interosseous wiring is recommended when there is marked displacement of fragments or separation of suture lines. This procedure permits anatomical alignment and permanent fixation.

7. Nonrecognition and delayed or inadequate treatment may lead to the serious sequelae of diplopia, enophthalmos, facial asymmetry with marked cosmetic defects, and associated psychic problems, as well as improper mandibular function and malocclusion.

Summary

A group of pictorial case reports of fractures about the orbit is presented which illustrates the various clinical and roentgenologic aspects of diagnosis and methods of treatment. The varying techniques of management of the individual fracture cases

presented here are the result of the cooperation of the ophthalmologist, the oral surgeon, and the rhinologist.

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Perfusion of Human Eyes with Latex Microspheres

SARA J. KARG, M.A.; LEVON K. GARRON, M.D.; M. LYNETTE FEENEY, A.B., and W. K. McEWEN, Ph.D., San Francisco

In a previous study[1] we visualized by stereomicroradiographic techniques the filtration apparatus of the human eye. These techniques were valuable in confirming the existence of an open pathway between the anterior chamber and the episcleral venous system. The perfusion of these pathways with a radiopaque solution of thorium dioxide (Thorotrast) revealed both the intricate anastomosing network of vessels extending to the episclera and the elaborate vascular arcade in the peripheral cornea. However, this method did not show conclusively the openings into and out of Schlemm's canal, nor did it yield precise quantitative data on the number and size of these channels. It appeared that a different method would be required for such determinations.

In vascular research the technique of perfusion with graded spheres has been useful in determining the size of blood vessels.[2] It seemed reasonable to suppose that this method would be applicable to the sizing of the exit channels of the eye if sufficiently small nondeformable spheres of uniform diameter were available in a range of sizes. The Dow Chemical Company and Dr. J. W. Vanderhoof furnished us with special research samples of graded latex microspheres.

Materials and Methods

For these experiments, human eyes were obtained from the eye bank. Each eye was placed on an annular plastic ring which was seated in a funnel as shown in the Figure. The funnel selected for this purpose had ridges on its inner conical surface which permitted liquid to flow between the plastic ring and the funnel wall. A 30-guage needle was inserted into the anterior chamber through the cornea, and the aqueous was replaced with the material to be perfused. The needle was then connected to a reservoir of perfusion fluid contained in a 2 ml. pipet graduated in 0.01 ml.

A constant hydrostatic pressure of 6.8 cm. H_2O (5 mm. Hg) was maintained by positioning the pipet horizontally at the appropriate height. This pressure was chosen as most nearly representing the differential between intraocular and episcleral venous pressures.[3] As the perfusion fluid passed through the episcleral venous plexes to the scleral surface, it was flushed down the funnel into a centrifuge tube by means of washing the eye with liquid petrolatum. At hourly intervals the sample in the centrifuge tube was spun at low speed to coalesce and separate the aqueous droplets from the oil. The water-layer was agitated with a small glass rod to resuspend any latex particles in the perfusate.

An aliquot of this water-layer was examined microscopically for the presence of particulate matter. An estimate of the concentration of latex spheres was obtained by counting the particles in a hemocytometer. This estimate was compared with the similarly estimated concentration of the spheres in the original perfusion fluid; when the concentration appeared to be approximately the same after perfusion, it was recorded as +++; when slightly less, it was recorded as ++; and when markedly less, it was recorded as +. The apparatus assembled for a typical experiment is shown in the Figure.

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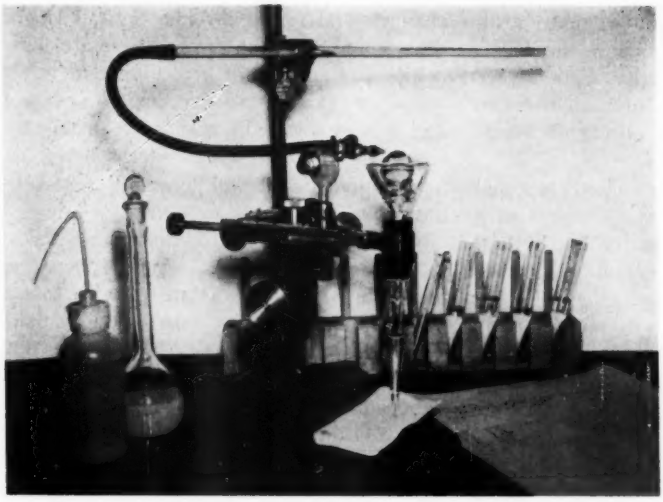

Apparatus assembled for a typical perfusion experiment.

The commercial samples of latex spheres had diameters of $0.511 \pm 0.0074\mu$ and $1.171 \pm 0.013\mu$; three experimental samples had diameters of 1.8μ, 3.0μ, and 5.6μ. The deviations from the mean in the sizes of the experimental samples were not given, but microscopic examination indicated the same very high degree of uniformity that characterized the commercial samples.

The latex suspensions were diluted with isotonic saline to obtain a suspension of particles with a concentration of about 4000 per microliter, except for the 0.511μ particles, which were diluted to about 200,000/μl.

Results and Comment

Twelve eyes were perfused with variously sized latex microspheres. The results are summarized in the Table. The duration of perfusion was in most cases from 3 to 5 hours, and the spheres usually first appeared in either the first- or the second-hour sample. In two eyes (Eyes 12 and 116) the perfusion time was prolonged to a total of nine and seven hours, respectively, the spheres

Perfusion of Normal Eyes with Latex Microspheres

Eye No.	Age of Donor	Elapsed Time *	Latex Size, μ.	Average Rate of Infusion, μl/Min.	Duration of Perfusion, Hr.	Latex Found	Time of First Appearance, Hr.
528	69	72	0.5	2.0	4	+++	1
419	59	3	1.17	3.3	3	+++	2
420	59	23	1.17	1.4 †	4	+++	1
714	51	40	1.17	2.2	3	+++	2
12	87	24	1.8	1.7	9	+	5
111 ‡	59	23	1.8	1.9	4	++	2
26	85	27	1.8	1.2	3	+++	2
116	22	44	3.0	2.5	7	++	6
131	71	3 §	3.0	1.5	4	++	2
26a	85	23	3.0	2.0	5	+	2
523	62	6	5.6	1.9	3	—	—
1017	63	53	5.6	2.6	4	—	—

* Time in hours from death to perfusion.
† Needle clogged for short period.
‡ Lamellar corneal section removed.
§ Enucleated at surgery.

first appearing in the samples taken after five and six hours. As shown in the Table, the average rates of infusion were of the same magnitude, the rate of each infusion remaining nearly constant during the entire time of the run.

Usually the quantity of fluid collected from the outside of the eye was less than the amount that went into the eye. Small losses may be due to evaporation. In accounting for the larger losses, the following mechanisms may be taken into consideration: (*a*) imbibition of fluid and swelling of tissues, (*b*) mechanical stretching of the sclera, and (*c*) gradual unfolding of inadvertent indentations in the globe. An extreme example of such loss is Eye 116, in which there was a constant inflow of 2μl. to 3μl. per minute for six hours before fluid was collected from the outside of the eye.

This diminution in the amount of fluid reaching the outside of the eye probably explains why the microspheres are usually found in the second-hour sample. The small amount of fluid usually collected in the first hour was that material contained in the exit channels of the eye, which was flushed out ahead of the perfusing liquid. This explanation is less satisfactory in explaining the late appearance of latex spheres in the case of Eye 12, since liquid, apparently in excess of that contained in the exit channels, was collected from the outside of the eye before the microspheres appeared. An enclosed system of perfusion is being developed [4] in an attempt to control the factors responsible for these losses.

Huggert [5,6] perfused human eyes with heterodispersed chromic phosphate particles and with bacteria in attempts to determine the size distribution of the exit channels. The agglomeration of the particles of such materials constituted a difficulty, but Huggert believed that he could measure the individual crystals in an agglomerate. Very few crystals passed that were greater than 2.5μ, but he recorded maximum particle sizes of 4.0μ, 2.0μ, 5.0μ, and 4.8μ. He used perfusion pressures of from 40 to 50 mm. Hg, and thus he may have distorted the exit channels and forced through crystals larger than would normally pass. There are difficulties and sources of error inherent in all perfusion methods so far devised, but we feel that we avoided a number of pitfalls by using the graded latex microspheres as perfusion material and by using relatively physiologic perfusion pressures.

In reporting a microradiographic study of the inner wall of Schlemm's canal in human eyes, François [7] stated that he found no entrances into the canal greater than 2.25μ. He did not perfuse these eyes, but withdrew aqueous and then injected a radiopaque iodine contrast solution (Angiopac). The amount injected was 0.1 ml. more than the amount withdrawn. Passage of the radiopaque material into the canal was determined by examination of subsequent radiographs.

In the present study, particles 1.2μ in diameter and smaller passed readily out of the eye, while particles 5.6μ in diameter were stopped (Table). There was some interference with the passage of the 1.8μ and 3.0μ particles, since the concentrations were noticeably lower in the perfusion samples than in the original perfusion fluid.

These experiments were designed to yield information on the size distribution curve of the exit channels. It was anticipated that the size of the largest single particle to perfuse would give the upper limit of this distribution curve, while the size of the largest particle to perfuse freely, without any change in concentration, would indicate the lower limit of the curve. On this basis, it could be concluded that the upper limits lay between 3.0μ and 5.6μ and the lower limits, between 1.2μ and 1.8μ. The shape of the distribution curve between these limits must await quantitative determinations. It is of interest that Huggert,[8] measuring the resistance of the outflow channels by perfusing with isobutyl alcohol, the surface tension of which differs from that of aqueous humor, found a narrow size distribution curve for the exit channels of human eyes. The peak of this curve was less than 1μ.

Summary

Twelve eyes were perfused with graded latex microspheres of various sizes. Particles 1.2μ in diameter and smaller passed through the eye without appreciable loss in concentration. There was some interference with the passage of the 1.8μ and the 3.0μ particles, as they emerged noticeably less concentrated than in the original perfusion fluid. Particles 5.6μ in diameter did not perfuse.

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Therapeutic Habits in Ophthalmology

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During the past decade a large number of new preparations have been added to the ophthalmologist's therapeutic armamentarium. For that reason it seemed that a survey of therapy employed by ophthalmologists today in everyday practice would be of interest. As a result, a questionnaire was circulated, and its results were compiled for presentation in this paper.

This questionnaire was mailed to all ophthalmologists and eye, ear, nose, and throat specialists throughout the United States.* In the questionnaire each physician was asked to state what treatment he usually prescribed for the following selected indications: chronic uveitis (anterior or posterior choroiditis), severe conjunctivitis, acute iritis, vernal catarrh, and nonspecific keratitis. The physician was also asked to state whether he ever employed oral, intramuscular, or intravenous corticotropin (ACTH) or corticosteroids; what he considers the principal indication for such therapy; how many days constitute an average course of therapy, and whether he manages such treatment himself or refers it to a specialist. Seven thousand one hundred forty-three questionnaires were mailed out. One thousand seven hundred forty, or 24.4 %, usable replies were received.† The final tabulations contained responses from each of the 48 states, the District of Columbia, and Alaska, with a concentration of replies from the Middle Atlantic, East, North, Central, and Pacific states.

All percentage figures shown in the following tables are based upon the original 1740, the total number of usable replies.

The large number of physicians employing corticosteroids or corticotropin in the treatment of chronic uveitis was surprising in view of conversations with hundreds of

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From the Department of Surgery (Ophthalmology), New York Hospital, and the Cornell University Medical Center, and the L. Margulyes League.

* Technical assistance was given by Alberta C. Roon, B.A., Management Research Department, Schering Corporation, Bloomfield, N. J.

† According to Fisher-Stevens Co., there are 3129 practicing ophthalmologists in the U. S. under 65 years of age and 1906 practicing E. E. N. T. specialists under age 65. It is likely that the replies came from these two groups.

TABLE 1.—*In Treating Chronic Uveitis, What Therapy Do You Usually Prescribe?*

Medication Prescribed	Total		Type of Application							
			Topical		Systemic		Both		No Answer	
	No.	%	No.	%	No.	%	No.	%	No.	%
Corticosteroids	1,238	71.2	231	13.3	358	20.6	543	31.2	106	6.1
Atropine	503	28.9								
Antibiotics	256	14.7	21	1.2	118	6.8	67	3.8	50	2.9
Foreign protein	234	13.4								
Corticotropin (ACTH)	151	8.7								
Combinations (antibiotics and corticosteroids)	110	6.3	61	3.5	11	0.6	19	1.1	19	1.1
Other (more than 13 different therapies)	469	27.0								
No answer	180	10.3								
Base	1,740	100.0								

ophthalmologists during the past several years. Our impression has been that a significant percentage of ophthalmologists hesitate to employ systemic corticosteroids or corticotropin. Unfortunately, there was not room in the questionnaire, without making it too lengthy, to ask for the dosage employed. The impression was that a large number of ophthalmologists employ dosage which I would consider inadequate. With this in mind, a subsequent smaller survey was conducted during the Postgraduate Course at Gill Memorial Hospital in Roanoke, Va. At that time a fairly large audience of ophthalmologists from all over the United States was given a questionnaire in which they were asked whether they had had any patients during the past year who had needed systemic corticosteroids. If the answer was yes, they were then asked to indicate which compounds were used and in which conditions the medication was employed. They were also asked to state the initial dosage and the number of days during which this dosage was employed, as well as the maintenance dose and the approximate number of days during which this was employed. They were also asked whether "a routine cut-off point was used during systemic therapy." The last question on this survey was whether or not the physician was one of the group who had returned the original survey questionnaire.

A total of 119 men, approximately 70% of those present in the conference room, returned the questionnaire. Although I am possibly incorrect, I assume that a large majority of those who did not return the questionnaire refrained because they do not use corticosteroids. Ninety-seven answered "yes," and 22 stated that they did not have any such patients during the past year. Of this "yes" group, only 10 employed corticotropin without any of the adrenal corticosteroids. The others employed steroids or steroids and corticotropin. The indications for corticosteroid therapy here were approximately the same as those in the larger survey. Of the group employing corticosteroids, 7 used initial doses of 5 to 10 mg. per day; 8 employed 10 mg. per day as the initial dose; 17 employed 15 mg. per day, and 20 employed 20 mg. per day as the initial dose. This represented the bulk of the persons stating their initial dosage, which is an inadequate amount. Nineteen employed the adequate dosage, 30 mg. per day, initially. More than half of the group using corticotropin employed an initial dosage of 40 units. Approximately half this group employed 40 units as a maintenance dosage of corticotropin, and the majority of the other half employed approximately 20 units as a maintenance dosage. Five indicated a preference for intravenous corticotropin. In this admittedly small group from whom statistics concerning dosages were gathered, the majority used doses which were either inadequate or two-thirds of what I consider adequate. Twenty-seven ophthalmologists kept their patients at this level of initial dosage for from 5 to 9 days, and 13, for

TABLE 2.—*In Treating Severe Conjunctivitis, What Therapy Do You Ususally Prescribe?*

Medication Prescribed	Type of Application									
	Total		Topical		Systemic		Both		No Answer	
	No.	%	No.	%	No.	%	No.	%	No.	%
Antibiotics	1,019	58.6	708	40.7	57	3.3	132	7.6	122	7.0
Sulfonamides	550	31.6	417	24.0	13	0.7	28	1.6	92	5.3
Combinations (antibiotics and corticosteroids)	407	23.4	347	19.9	2	0.1	8	0.5	50	2.9
Corticosteroids	232	13.3	177	10.2	6	0.3	14	0.8	35	2.0
Other (more than 10 different therapies)	352	20.2								
No answer	91	5.2								
Base	1,740	100.0								

TABLE 3.—*In Treating Acute Iritis, What Therapy Do You Usually Prescribe?*

Medication Prescribed	Type of Application									
	Total		Topical		Systemic		Both		No Answer	
	No.	%	No.	%	No.	%	No.	%	No.	%
Corticosteroids	1,343	77.2	634	36.4	140	8.1	430	24.7	139	8.0
Atropine	936	53.8								
Antibiotics	279	16.0	50	2.9	75	4.3	87	5.0	67	3.8
Foreign protein	199	11.4								
Combinations (antibiotics and corticosteroids)	186	10.7	132	7.6	2	0.1	16	0.9	36	2.1
Physical therapy	115	6.6								
Other (more than 13 different therapies)	403	23.2								
No answer	54	3.1								
Base	1,740	100.0								

approximately 20 days. In my opinion, this represents too short a period, for the most part, for an initial dose which in most cases is equivalent to only 10 to 20 mg. of prednisone or prednisolone.

The large percentage of ophthalmologists, 14.7%, employing antibiotic therapy in chronic uveitis is noteworthy, especially in view of the fact that the indications for such therapy are tenuous.

In the treatment of severe conjunctivitis, 90% of the responding ophthalmologists reported employing either antibiotics or sulfonamides. Only 13% employed corticosteroids, and approximately 25% used combinations of corticosteroids and/or sulfonamides or antibiotics.

In the treatment of acute iritis, 47% employed corticosteroids and 10% utilized combinations of corticosteroids and antibiotics. The fact that only 54% stated that they employed atropine is somewhat surprising in view of the fact that this has been entrenched for a long time as the basic therapy in the treatment of acute iritis. It is my feeling that when steroid therapy is employed atropine is not essential in the treatment of acute iritis unless adhesions are present or being formed.

In the treatment of acute choroiditis approximately 68% of the reporting ophthalmologists employed corticosteroids and 13% used corticotropin. In most of these instances steroid therapy is employed systemically as reported. Again, over 18% reported the employment of antibiotics. The indications for the employment of antibiotics here are not very clear.

TABLE 4.—*In Treating Acute Choroiditis, What Therapy Do You Usually Prescribe?*

Medication Prescribed	Type of Application									
	Total		Topical		Systemic		Both		No Answer	
	No.	%	No.	%	No.	%	No.	%	No.	%
Corticosteroids	1,186	68.2	100	5.8	664	38.2	286	16.4	136	7.8
Atropine	447	25.7								
Antibiotics	323	18.5	18	1.0	180	10.3	51	2.9	74	4.3
Corticotropin (ACTH)	218	12.5								
Foreign protein	217	12.5								
Combinations (antibiotics and corticosteroids)	80	4.6	35	2.0	19	1.1	11	0.6	15	0.9
Other (more than 14 different therapies)	359	20.6								
No answer	183	10.5								
Base	1,740	100.0								

TABLE 5.—*In Treating Vernal Catarrh, What Therapy Do You Usually Prescribe?*

Medication Prescribed	Type of Application									
	Total		Topical		Systemic		Both		No Answer	
	No.	%	No.	%	No.	%	No.	%	No.	%
Corticosteroids	1,283	73.7	1048	60.2	18	1.0	66	3.8	151	8.7
Antihistamines	286	16.4	121	6.9	66	3.8	51	2.9	48	2.8
Combinations (antibiotics and corticosteroids)	194	11.2	158	9.1	5	0.3	1	0.1	30	1.7
Antibiotics	86	4.9	55	3.2	6	0.3	7	0.4	18	1.0
Other (more than 16 different therapies)	352	20.2								
No answer	104	6.0								
Base	1,740	100.0								

In the treatment of vernal catarrh, the bulk of the ophthalmologists reporting employed either corticosteroids, antihistaminics, or combinations. This is obviously in line with the current feeling that vernal catarrh is probably allergic in basis. Only 5% reported the employment of antibiotics. If vernal catarrh is based on an allergy principle, antibiotics would not appear to be indicated. The low percentage reported here would be in line with that feeling.

In the treatment of nonspecific keratitis, 46% employed corticosteroids; 27%, antibiotics; 14% employed combinations of antibiotics and steroids, and 6.6% employed sulfonamides. The question was so worded as to exclude dendritic (herpes simplex) keratitis.

Table 7 shows that 57% stated that they treated more than 12 cases a year with corticosteroids, 40%, less than 12 cases a year with corticosteroids, while 4% did not answer this question.

In answer to the question "how many days are average courses of systemic therapy?" 514 respondents required 2 to 7 days and 748 respondents required 8 to 14 days. In answer to the same question in reference to the average course of therapy in chronic conditions, the largest concentration of 428 replies was in the 30- to 60-day category, whereas 273 indicated between 15 and 21 days. There was a total of 1586 replies here.

It was interesting that the bulk of the respondents employed trade names rather than generic names. It has long been my impression that many physicians in an audience may not know what the speaker is referring to when he does not employ

TABLE 6.—*In Treating Nonspecific Keratitis, What Therapy Do You Usually Prescribe?*

Medication Prescribed	Type of Application									
	Total		Topical		Systemic		Both		No Answer	
	No.	%	No.	%	No.	%	No.	%	No.	%
Corticosteroids	806	46.3	580	33.3	35	2.0	68	3.9	123	7.1
Antibiotics	465	26.7	348	20.0	20	1.2	32	1.8	65	3.7
Atropine	309	17.8								
Combinations (antibiotics and corticosteroids)	241	13.8	187	10.7	2	0.1	3	0.2	49	2.8
Sulfonamides	116	6.6	84	4.8	4	0.2	4	0.2	24	1.4
Physical therapy	93	5.3								
Other (more than 14 different therapies)	362	20.8								
No answer	309	17.8								
Base	1,740	100.0								

TABLE 7.—*Results of Questionnaire Concerning Corticotropin or Corticosteroid Therapy*

In your practice, do you ever use oral, intramuscular, or intravenous corticotropin or corticosteroids?

	No.	%
Yes	1,586	91.1
No	154	8.9
Total	1,740	100.0

If yes, which do you use?

ACTH (corticotropin)	435	27.4
Corticosteroids	389	24.5
Meticorten (prednisone)	223	14.1
Prednisolone	122	7.7
Cortisone	75	4.7
Prednisone	69	4.4
Hydrocortisone	55	3.5
Meticortelone (prednisolone)	41	2.6
ACTHAR (JEL) (corticotropin)	32	2.0
Hydrocortone (hydrocortisone)	27	1.7
Neo-Delta-Cortef (prednisolone acetate and neomycin sulfate)	20	1.3
Sterane (prednisolone)	13	0.8
Cortone (cortisone)	10	0.6
Neo-Cortef (hydrocortisone acetate and neomycin sulfate)	6	0.4
Metimyd (prednisolone acetate and sulfacetamide sodium)	5	0.3
Cortef (hydrocortisone)	3	0.2
Terracortyl	3	0.2
Metreton (prednisolone acetate and chlorprophenpyridamine-gluconate)	2	1.0
Achromycin (tetracycline)	1	1.0
Antibiotics	1	1.0
Zinc sulfate	1	1.0
Miscellaneous	27	1.7
"All"	50	3.2
"Depends"	8	0.5
No answer	443	27.9
Base	1,586	100.0

Type of application

Oral	550	
Intramuscular	129	
Intravenous	81	
Oral and muscular	90	
Oral and intravenous	19	
Intramuscular and intravenous	31	
"All", "all three"	94	
No answer	624	
Total No. of medications	1,618	
Base: No. who listed medication (s)	1,143	
More than 12 cases yearly	901	56.8
Less than 12 cases yearly	623	39.3
No answer	62	3.9
Base	1,586	100.0

What do you consider the principal indications?

	Total	
	No.	%
Uveitis	600	37.8
Iritis, iridocyclitis, cyclitis	291	18.3
Choroiditis	274	17.3
Posterior segment conditions (includes retinitis, retinopathy, central serous, intraocular)	245	15.4
Severity of conditions being treated, acuteness, danger to vision and to central acuity	210	13.2
Allergy, vernal catarrh, vernal conjunctivitis	183	11.5
Anterior segment conditions (includes "inflammation" unless defined as posterior or deep-seated)	166	10.5
Neuritis, optic	153	9.6
Failure, ineffective topical and ordinary treatment	124	7.8
Trauma: injury, operative, postoperative	72	4.5
Keratitis, corneal disease, ulcer	70	4.4
Sympathetic ophthalmia	69	4.4
Scleritis, episcleritis	29	1.8
Pain, to reduce pain	20	1.3
Herpes zoster	17	1.1
Conjunctivitis (other than allergic or vernal), mucous membrane conditions	16	1.0
Glaucoma	12	0.8
Endophthalmitis	5	0.3
Orbital	4	0.3
Many, wide, almost every case, "infections"	36	2.3
Miscellaneous	142	9.0
No answer	151	9.5
Base	1,586	100.0

How many days are average course of systemic therapy in acute conditions?

Days	No.	%
2	3	0.2
3	26	1.6
4	66	4.2
5	113	7.1
6	110	6.9
7	196	12.3
8	90	5.7
9	54	3.4
10	262	16.5
11	47	3.0
12	64	4.0
13	12	0.7
14	219	13.8
15	46	2.9
16	3	0.2
17	9	0.6
18	32	2.0
19	3	0.2
20	30	1.9
21	44	2.8
22	4	0.2
23	5	0.3
24	1	0.1
25	5	0.3
28	4	0.2
29	1	0.1
30	25	1.6
31	1	0.1
32	1	0.1
35	3	0.2
38	1	0.1
45	3	0.2
"1 wk. to 6 mo."	1	0.1
"2 wk. to several months"	1	0.1
Indefinite answer	48	3.0
None	2	0.1
No answer	51	3.2
Total	1,586	100.0

How many days are average course of systemic therapy in chronic conditions?

Days	No.	%
3	1	0.1
4	6	0.4
5	14	0.9
6	9	0.6
7	19	1.2
8	11	0.7
9	9	0.6
10	48	3.0
11	15	0.9
12	23	1.4
13	7	0.4
14	109	6.9
15	32	2.0
16	6	0.4
17	13	0.8
18	39	2.4
19	5	0.3
20	59	3.7
21	119	7.5
22	14	0.9
23	10	0.6
24	3	0.2
25	72	4.5
26	5	0.3
27	2	0.1
28	20	1.3
29	1	0.1
30	247	15.6
31	5	0.3
32	6	0.4
33	1	0.1
35	12	0.7
37	2	0.1
38	8	0.5
39	1	0.1
40	12	0.7
42	12	0.7
45	58	3.6
47	1	0.1
49	3	0.2
50	6	0.4
52	1	0.1
53	1	0.1
55	2	0.1
56	1	0.1
60	59	3.7
65	1	0.1
66	1	0.1
72	1	0.1
73	1	0.1
75	13	0.8
80	1	0.1
90	26	1.6
93	1	0.1
100 days or more	29	1.8
Indefinite	205	12.9
No answer	198	12.5
Total	1,586	100.0

Do you ever go over 30 days of systemic treatment?

	No.	%
Yes	929	58.6
No	651	41.0
Not stated	6	0.4
Total	1,586	100.0

If yes, do you manage the treatment yourself or do you refer it to a specialist?

	No.	%
Manage it myself	299	32.2
Refer it to a specialist	325	35.0
"Both, sometimes"	198	21.3
In consultation	105	11.3
No answer	2	0.2
Total	929	100.0

trade names. On the other hand, the disadvantages and implications of employing trade names are rather obvious. Nevertheless, this fact must be borne in mind. Perhaps when one is speaking on a subject, it might be well to give the generic name as well as a list of trade names on slides which can then be viewed by the audience.

The bulk of the antibiotics employed in treating the various conditions fell into the tetracycline group. Three and one-half per cent employed streptomycin in chronic uveitis, as compared with only seven per cent in severe conjunctivitis. Prednisone and prednisolone were the favorite steroids.

A number of letters were received along with the surveys, as well as written comments on the surveys themselves. It is unfortunate that these cannot be included, since many were interesting. However, one, which came from an ophthalmologist in a small university city which has a medical center, is interesting in that it exemplifies physician stated that during the past year he had two patients who became blind as the spirit of a number of comments. This a result of uveitis. He then went on to state that he has never employed corticosteroid therapy because he "had never had a patient who needed it." In view of the fact that the bulk of the ophthalmologists reporting, as well as the bulk of ophthalmologists who have written on the subject of steroid therapy, believe that uveitis is the prime indication for steroid therapy, this type of thinking is paradoxical. One wonders how many other patients have become similarly incapacitated as a result of failure to employ this indicated therapy.

Approximately 50% of those reporting both in the small group at Gill Memorial Hospital and in the large survey group considered the uveitides the prime indications for steroid therapy.

From the comments written on the surveys as well as from many of the commenting letters which were enclosed, one gathers the impression that a large segment of those who do use corticosteroid therapy systemically do so only after everything else has failed or else late in the disease. Many of those who are interested in the field of corticosteroid therapy feel that this form of treatment should be employed as soon as the diagnosis of inflammation or allergy is made. Where no specific ocular or systemic contraindications exist, systemic corticosteroid therapy should be employed immediately rather than delayed until too late. Furthermore, the doses should be adequate to do the job. In the case of prednisone or prednisolone this means 30 to 40 mg. per day initially for as many days as is necessary to secure a definite improvement. After this, medication may be slowly tapered off over that period of time during which the disease can still be suppressed constantly as the dose is slowly being lowered until both the disease and the medication are eventually eliminated. This is certainly the course in acute disease. In the treatment of chronic intraocular inflammation or chronic external inflammation of the eye, it is necessary to maintain a suppressing level of dosage for as long a period as the disease persists. This may mean for an indefinite period. If dosage adequate to suppress the disease is not employed in the very beginning, good control is impossible and poor results will eventuate. This, then, is the *sine qua non* of steroid therapy, to employ enough for as long as it is required to do the job at hand.

While it is admitted that this survey is inadequate in many respects and certainly could not replace a personal interview with the same number of men or even one-third or one-half that group, the results found, nevertheless, are very interesting in that they point to the therapeutic habits of American ophthalmologists. It is admitted that many conclusions may be drawn from the same statistics. For that reason my comments have been kept to a minimum. I feel that the data point up the facts that most ophthalmologists employ corticosteroid therapy, especially systemically, in inadequate amounts for too short a period of time, and often too late to alter the course of the disease.

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Streptococcal Serology in Uveitis

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The etiologic role of the streptococci in uveitis is predicated upon the high rate of association of endogenous uveitis, particularly of the nongranulomatous variety, with chronic foci of infection and with rheumatoid arthritis. The streptococci are the organisms most frequently found in foci and are the organisms usually responsible for the bacterial hypersensitivity displayed by rheumatoid arthritics.[1]

The dearth of clinical ocular tissue for direct laboratory examination makes us more dependent upon skin tests and serological studies for relating streptococcal infection to uveitis. Using both autogenous and 59 immunologically distinct stock streptococcal vaccines, Woods[1,2] found skin hypersensitivity in 85% of patients with nongranulomatous uveitis and in 27% of those with granulomatous uveitis. The objection has been raised, however, that this study did not form a random series and that it included a higher proportion of patients with a poor prognosis or recurrent attacks.[3]

Evidence of foregoing streptococcal infection may also be derived from the level of circulating antibody for streptococcal hyaluronidase and streptococcal hemolysin. The reports on these serologic tests in uveitis have lacked uniformity. Schone and Steen[4] and Smith and Ashton[5] reported antistreptolysin (ASL) titers for anterior uveitis only, whereas Leopold and Dickinson[6] and Witmer[7] reported the same for all types of uveitis without a breakdown into various groups. The upper limit of normal ASL titer has been variously and arbitrarily stated as 100 (Smith[5]) or 166 (Witmer[7]) or has been compared with a normal geometric mean titer of 36 (Leopold[6]). Antistreptohyaluronidase (ASH) titers were done by the mucin-clot-prevention test in Leopold and Dickinson's study[6] and by the much more complicated turbidimetric test in Hallett, Leopold, and Inwald's work.[8]

Clinical Material

As part of a wider study of uveitis this report relates our experiences with steptococcal serologic tests in 136 consecutive and unselected cases of uveitis referred to us from certain ward and private services at the Wills Hospital. In addition to a full history and thorough physical and x-ray examinations, each case was subjected to a battery of laboratory tests. The latter included all the usual routine studies plus streptococcal serological tests on blood and, in a few instances, on aqueous. The blood and aqueous specimens were obtained within the first few days of hospitalization. A second blood specimen was obtained in 86 cases just prior to discharge from the hospital, in most instances at a time of considerable clinical improvement.

Table 1 shows a breakdown of the 136 cases into types of uveitis and probable etiology. Where posterior involvement occurred we chose to beg the difficult question of whether it was granulomatous or not. Also, in a study of this sort, where we are attempting to assess the value of a laboratory procedure, such as investigation of streptococcal serology, in relation to the etiology of uveitis, we avoided any consideration of the

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TABLE 1.—*Diagnostic Groups of the Cases Studied*

Associated General Disease	Type of Uveitis				
	Anterior				
	Gran.	Non-gran.	Posterior	Pan.	Total
Foci	7	27	12	18	64
Rheumatic	3	12	2	1	18
Tuberculosis			3	1	4
Sarcoid	2				2
Allergy	1	1			2
Sympathetic	1				1
Phacogenetic		1			1
Harada			2		2
Herpes simplex	1				1
Toxoplasmosis			1		1
No associated disease	7	13	11	9	40
Total	22	54	31	29	136

tests themselves in assigning a probable etiology in any specific case of uveitis. Rather, our choice of etiology was strongly determined by history and physical and x-ray examinations.

The study group consisted of 51 females and 85 males. The age range was from 18 months to 80 years, with a mean age of 39.6 years. These figures are summarized in Table 2.

Methods

Of the several methods available for ASH testing we decided to use the mucin-clot-prevention test in order to compare our results with those of a previous study [6] in which the same test was employed. The reagents for the test were supplied by Dr. T. N. Harris, Children's Hospital, Philadelphia, and the procedure followed was the one performed by him for us in the previous study.[9] This method also has the advantage of ease of performance as compared with the turbidimetric method, which we used in our second study [8] on this antibody.

The antistreptolysin "O" assays were performed with the reagents and by the technique recommended by Rantz and Randall.[10] The titers are expressed in Todd units. Each such unit is the reciprocal of the highest dilution of serum showing no hemolysis.

Results

In order to determine the level of the titers in a normal population we procured, from the local Red Cross, blood specimens from 300 healthy blood donors. The geometric mean titer for ASH was 35 units per milliliter, and the arithmetic mean titer for ASL was 31 Todd units per milliliter. These figures are in accord with averages for similar healthy control groups studied by Harris and Harris. The percentage frequency distributions of these titers are listed in Tables 3 and 4.

Consideration of all the cases of uveitis as a group reveals the geometric mean titer of ASH to be 73 and the arithmetic mean titer of ASL to be 24. The total number of cases with second blood specimens give respective mean titers of ASH, 91 and ASL, 27.

In 82 of our cases a streptococcal etiology was suspected because of history and physical and x-ray examinations. The respective mean ASH and ASL titers were 78 and 26. In 54 of these cases second blood specimens were obtained, with respective titers of 92 and 25.

The claim that anterior uveitis shows the highest percentage of streptococcal infection prompts consideration of our 76 cases of this type of uveitis. Since 7 of these were due to nonstreptococcal diseases, 69 cases were left for evaluation. The respective mean titers were ASH, 74 and ASL, 28. In

TABLE 2.—*Age Range of Study Group*

Age, Yr.	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-80	Total	Mean
Female	2	3	8	10	8	9	9	2	51	--
Male	0	8	21	24	16	8	5	3	85	--
Total	2	11	29	34	24	17	14	5	136	39.6

TABLE 3.—*Percentage Frequency Distribution and Geometric Mean Titers of ASH in Normal and in Uveitis Patients*

		Uveitis												
		Total		Suspected Strep.		Anterior		Ant. Nongr.		Ant. Gran.		Post.	Pan.	
Titer	Normal 300 †	(1st)* 136	(2nd) 85	(1st) 82	(2nd) 54	(1st) 69	(2nd) 46	(1st) 54	(2nd) 37	(1st) 22	(2nd) 15	(1st) 31	(1st) 29	(2nd) 21
16	40.0	16.9	18.8	14.6	18.6	16.0	19.6	14.8	16.3	27.4	33.3	25.8	3.4	14.4
24	16.0	16.9	14.1	17.1	16.7	11.6	19.6	16.7	18.9	4.5	13.3	12.9	31.0	9.5
48	16.2	11.8	9.4	9.8	5.5	16.0	4.3	16.7	5.4	9.1	6.7	9.7	6.9	19.0
96	15.0	24.3	18.8	28.1	24.0	31.9	21.8	25.9	27.0	40.8	6.7	22.6	6.9	9.5
192	10.0	15.4	18.8	14.6	11.1	10.1	17.5	12.9	13.5	0.0	26.6	19.4	31.0	19.0
384	1.4	11.0	7.1	13.4	9.3	11.6	4.3	11.1	5.4	13.7	0.0	6.4	13.9	14.3
768	0.7	1.5	7.1	0.0	9.3	1.4	4.3	0.0	5.4	4.5	6.7	3.2	0.0	14.3
1,536	0.7	2.2	5.9	2.4	5.5	1.4	8.6	1.9	8.1	0.0	6.7	0.0	6.9	0.0
IRD		61.8	63.0	63.6	62.3	67.5	60.5	63.0	63.0	63.3	54.8	59.1	63.3	65.2
Geometric mean titer	35	73	91	78	92	74	83	70	89	69	69	69	100	100

* Numbers in parentheses indicate relative number of specimen.
† Column across represents total number of specimens.

this group 46 second specimens had respective mean titers of 74 and 28.

All the above results along with percentage frequency distributions are listed in Tables 3 and 4, which also include similar data for the anterior nongranulomatous, anterior granulomatous, posterior, and panuveitis cases.

Comment

Obviously the ASL mean titers indicate no significant rise for any group of uveitis cases. The geometric mean ASH titers, on the other hand, are moderately but definitely increased over the expected titer for the normal population. No single group of cases, however, is favored with a significantly higher titer than any other group, nor does serial titration indicate significant change in titer as the disease passes from an active into a quiescent stage.

The significance, or lack thereof, of the mean titers is corroborated by calculating

TABLE 4.—*Percentage Frequency Distribution and Arithmetic Mean Titers of ASL in Normal and in Uveitis Patients*

		Uveitis												
		Total		Suspected Strep.		Anterior		Ant. Nongr.		Ant. Gran.		Post.	Pan.	
Titer	Normal 300 †	(1st)* 134	(2nd) 84	(1st) 82	(2nd) 54	(1st) 68	(2nd) 46	(1st) 53	(2nd) 37	(1st) 22	(2nd) 14	(1st) 30	(1st) 29	(2nd) 21
10	23.8	32.8	29.8	30.5	33.3	27.9	30.4	28.3	27.1	22.8	28.6	30.7	41.5	33.4
50	26.0	26.9	16.7	24.4	11.1	26.5	15.2	26.4	18.9	27.3	14.3	26.8	27.6	14.4
100	20.0	16.4	21.4	17.1	20.5	14.7	19.6	13.2	18.9	27.3	28.6	13.4	27.3	23.9
150	8.7	10.5	11.9	12.2	13.0	16.1	13.0	16.9	10.8	9.1	14.3	6.7	3.4	9.5
200	6.2	3.7	5.9	4.9	5.6	4.4	10.9	3.8	8.1	4.5	7.1	6.7	0.0	4.7
250	7.6	4.5	7.1	7.3	11.1	7.3	4.3	7.6	8.1	4.5	0.0	0.0	3.4	4.7
333	1.3	0.0	1.2	0.0	1.8	0.0	2.2	0.0	2.7	0.0	0.0	0.0	0.0	0.0
500	2.8	1.5	2.4	1.2	1.8	1.5	2.2	1.9	2.7	0.0	0.0	0.0	3.4	4.7
625	1.8	2.2	3.6	1.2	1.8	0.0	2.2	0.0	2.7	0.0	7.1	6.7	3.4	4.7
833	1.8	1.5	0.0	1.2	0.0	1.5	0.0	1.9	0.0	4.5	0.0	0.0	0.0	0.0
IRD		45.3	51.8	47.5	52.6	48.0	52.2	47.6	51.7	49.9	52.9	41.7	41.0	50.7
Arithmetic mean titer	31	24	27	26	25	28	28	27	29	31	35	21	20	25

* Numbers in parentheses indicate relative number of specimen.
† Column across represents total number of specimens.

TABLE 5.—*Comparative ASL Studies in Uveitis*

		ASL Mean Titers		
		No.	Uveitis	Control
Anterior Uveitis	Schone & Steen	105	119	74
	Smith & Ashton	89	88	60
	Present study	75	28	31
All Types of Uveitis	Leopold & Dickinson	63	48	33
	Witmer	53	104	63
	Present study	134	24	31

the index range difference (IRD). This percentage figure, as we previously pointed out,[8] has the same percentage of normal serums below it as the percentage of uveitis serums above it. Thus, an index of 50 would indicate a poor test, since half the uveitis serums would have titers above the index titer and half the normals would have titers below the index titer. Similarly, a titer of 100 would indicate an ideal test in which all the uveitis titers are above and all the normal titers below the index titer. Tables 3 and 4 also include the IRD for all groups.

Apparently streptococcal serologic studies are not a very fruitful source of investigation for relating streptococcal infections to uveitis. We feel that this is corroborated by careful assessment of other studies. Table 5 summarizes the recorded studies on ASL titers in uveitis. Though some of these results are suggestive, none are truly significant. The obvious variation in titer from one study to the next indicates that the tests done by different workers are not comparable titer for titer.

Table 6 summarizes the recorded studies on ASH titers in uveitis. It is readily apparent that the second study, which records our experiences with the turbidimetric method, is totally lacking in significance. The results of the first and present studies with the mucin-clot-prevention method, however, are very similar, as they should be, considering the identity of the materials and method from the same laboratory for each study. The IRD of 64.4 reported for the first study also compares closely to the figure of 61.8 obtained in the present study.

If we combine the first and present ASH groups into a single large group of 199 cases of uveitis, the increased geometric mean titer and IRD would suggest that these cases do not represent normal material with regard to serum antistreptohyaluronidase. The test must, however, be considered of low diagnostic significance in this particular group.

Witmer [11] recently reported his results on ASL examination of the aqueous. In 38 cases of uveitis, 28 were negative, with an average titer of 62, and 10 were positive, with an average titer of 240. We have had no experience with ASL in aqueous, but we have determined 25 ASH titers on aqueous from a representative group of eyes afflicted with uveitis. A uniformly low titer below 16 was found in all of them despite a range of blood serum titers in these cases from 16 to 1536. This may indicate that our method is not sensitive enough to demonstrate the presence of ASH in aqueous humor. It is more likely, however, that the blood-aqueous barrier is selective and easily prevents the passage of the large antibody molecule from the blood into the aqueous. It can certainly be deduced that local production within the eye itself of streptococcal antihyaluronidase is of no consequence, if not completely nil.

Summary

The serum levels of antistreptolysin "O" are of no significance in uveitis. The serum levels of antistreptohyaluronidase performed by the mucin-clot-prevention test are of low diagnostic significance in uveitis. No single diagnostic group of cases is favored with

TABLE 6.—*Comparative ASH Studies in Uveitis*

	ASH Mean Titers		
	No.	Uveitis	Control
Leopold & Dickinson	63	70	30
Hallett & Leopold	90	84	97
Present study	136	73	35

significantly higher titers than any other group. Serial titration reveals no significant change in titer as the disease passes from an active into a quiescent stage.

No antistreptohyaluronidase is demonstrable by the mucin-clot-prevention test in the aqueous of eyes afflicted with uveitis.

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Influence of General Anesthesia on Intraocular Pressure in Man

The Effect of Diethyl Ether, Cyclopropane, Vinyl Ether, and Thiopental Sodium

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Most studies of the effect of general anesthesia on intraocular pressure have been carried out in animals.[1,2] A decrease in intraocular pressure as a result of anesthesia has usually been found. However, there has been no systematic study of the effect of general anesthesia on intraocular pressure in a large series of normal human eyes. This problem is of particular importance in the case of small children in whom intraocular pressure can only be measured under general anesthesia.

This paper deals with the effect of diethyl ether, cyclopropane, vinyl ether, and thiopental sodium on intraocular pressure in a large series of patients.

Material and Methods

Both eyes of 70 patients undergoing short operative procedures were examined. The eyes in all cases were normal. The intraocular pressure was repeatedly measured immediately preceding the induction of anesthesia following premedication with morphine and atropine, at intervals during the course of anesthesia, and finally on recovery. A Schiøtz tonometer with a 5.5 gm. weight was used.

In 16 eyes of 11 patients tonography was performed using the Muller electronic tonometer connected to a Sanborn recorder. Measurements in 12 eyes were made the day before general anesthesia as well as during anesthesia. The two determinations were done at approximately the same hour of the day. In the four remaining eyes the control tonography was performed two to three hours before general anesthesia. The tonometric results were calculated according to the latest of Friedenwald's tables.

The anesthetic agents used were diethyl ether, cyclopropane, vinyl ether, and thiopental sodium (Pentothal Sodium). The gases were administered either by mask or endotracheal tube. Special care was taken to avoid pressure on the patient's eyes and to maintain a fully patent airway to prevent respiratory disturbances leading to straining and increased venous pressure. Endotracheal intubation was performed with the aid of succinylcholine to avoid cough or laryngospasm. The elevation of intraocular pressure produced by this drug is very transient.[3]

When ether was administered, ethyl chloride or nitrous oxide was used for induction and tonometry was started 10 to 15 minutes after onset of anesthesia. With cyclopropane and oxygen for induction and maintenance of anesthesia, tonometry was started 10 to 15 minutes after onset of anesthesia. With vinyl ether induction and maintenance, tonometry was started five minutes after the onset of anesthesia. Thiopental sodium was given as 0.2 to 0.5 gm. of a 2.5% solution intravenously to produce moderate to deep anethesia. Tonometry was started five minutes after the injection.

In addition to the tonometric determinations, the blood pressure, pulse rate, and pupillary size were recorded before and at intervals during the course of the anesthesia.

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Effect of Anesthetic Agents on Intraocular Pressure

	Eyes, No.	Av. Mean Pressure, Mm. Hg	Standard Deviation, Mm. Hg	Standard Error of Mean	Difference Between Means of Intraocular Pressure				Test of Significance of Difference				
					Normal	Cyclopropane	Diethyl Ether	Thiopental Sodium	Normal	Cyclopropane	Diethyl Ether	Thiopental Sodium
Normal	140	17.7	2.72	0.23	—	—	—	—	—	—	—	—
Cyclopropane	20	11.4	3.64	0.84	6.3	—	—	—	*P<0.001* *	—	—	—
Diethyl ether	32	12.0	2.14	0.38	5.7	0.6	—	—	*P<0.001*	0.4<*P*<0.5	—	—
Thiopental sodium	78	10.7	2.23	0.25	7.0	0.7	1.3	—	*P<0.001*	0.2<*P*<0.3	*P*<0.01	—
Vinyl ether	10	11.6	1.67	0.56	6.1	0.2	0.4	0.9	*P<0.001*	0.9<*P*	0.5<*P*<0.6	0.2<*P*<0.3

* Italicized values of *P* indicate statistically significant differences.

Tubocurarine chloride (curare) in a dose of 6 to 9 mg. was administered intravenously to five patients without general anesthesia. Tonography was performed on both eyes of each patient before and after treatment with curare.

Results

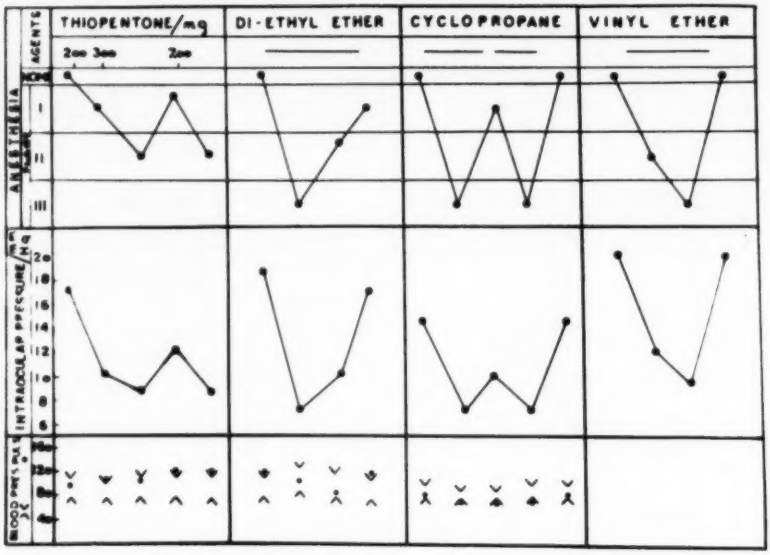
Each of the anesthetic agents tested caused a statistically significant decrease in intraocular pressure (Table). The extent of this decrease ranged from 5.7 mm. Hg with ether to 7.0 mm. Hg with thiopental as compared with an average initial pressure of 17.7 mm. Hg. There was no significant difference in the decreases caused by the various drugs, although the difference in decrease between ether and thiopental was on the border of significance.

The maximal decrease in intraocular pressure occurred when deep anesthesia was reached (Figure). With thiopental and vinyl ether this stage was usually reached five minutes after starting the anesthesia, and in the case of ether and cyclopropane, within 15 minutes.

Tonography showed that thiopental anesthesia caused a significant increase in the coefficient of facility of outflow from an average of 0.18 to 0.28 ($P=0.006$). With ether the increase in the coefficient of facility of outflow was significant, though to a less extent, increasing from an average of 0.21 to 0.28 ($P=0.05$).

The usual variations in pupillary size with change in depth of anesthesia were found. During deepest anesthesia, when the lowest intraocular pressure was recorded, mydriasis was most prominent. In most cases the blood pressure decreased by 10 to 20 mm. Hg during the course of the anesthesia.

Any respiratory disturbances during the course of anesthesia such as cough, laryngospasm, or straining, which raise venous pressure, resulted in a moderately prolonged increase in intraocular pressure. All cases in which such interference in smooth respi-



Correlation of depth of anesthesia with intraocular pressure.

ration occurred were therefore excluded from the series.

Curare caused a lowering of the intraocular pressure by 1.3 to 4.9 mm. Hg, with an average decrease of 2.8 mm. Hg. Tonography showed a 30% reduction of the flow of aqueous and an 18% decrease of the coefficient of facility of outflow following the administration of curare.

Comment

The results of this study indicate that the intraocular pressure during general anesthesia is significantly lowered. This factor should be taken into account when intraocular pressure is measured in children or other patients under general anesthesia.

A decrease in intraocular pressure due to thiopental anesthesia was also found by de Roetth and Schwartz.[4] They studied patients with simple glaucoma in whom the pressure fell by an average of 19 mm. Hg. Barbiturates were also found by Rubino and Esente[5] to lower the ocular tension in man. On the other hand, they reported that nitrous oxide, chloral hydrate, and diethyl ether caused transient increases in intraocular pressure. In our studies the latter lowered the intraocular pressure. However, Rubino and Esente did not give the exact data of their experiments or the number of patients examined.

Relaxation of the extraocular muscles as found in surgical anesthesia[6] is known to cause a drop of intraocular pressure. Paralyzing the extraocular muscles by curare as a rule produces a decrease of ocular tension, the range of which varies according to different authors.[7-10] In our experiments the intraocular pressure dropped by an average of 2.8 mm. Hg after intravenous injection of 6 to 9 mg. of curare. On the other hand, Snydacker et al.,[11] studying the effect of different anesthetics used in retrobulbar injection, came to the conclusion that there was no relation between the degree of paralysis of the extraocular muscles and the reduction of ocular tension.

While relaxation of the extraocular muscles under surgical anesthesia may play an important role in the lowering of the intraocular pressure, the increase of the coefficient of facility of outflow (C) found on tonography may indicate an additional fac-

tor effective in reducing the ocular tension. Studies on animals [2] and patients with simple glaucoma [4] corroborate our finding of an increased C under general anesthesia. This increase of C cannot be attributed to relaxation of the extraocular muscles, as C decreased by 18% after injection of curare.

A center for control of intraocular pressure has been demonstrated in the region of the hypothalamus.[12-16] It is accepted that under general anesthesia at the stage of complete sensory loss, regardless of the anesthetic agent used, the hypothalamus is depressed as are the cerebral cortex and related structures, including the nuclei of the extraocular muscles.[17] Thus, every drug employed in this study reduced the intraocular pressure if moderate to deep anesthesia was reached. It is interesting to speculate that C, which changes under general anesthesia, may be regulated by a central mechanism.

Summary

General anesthesia produced by drugs of different types lowered the intraocular pressure in a series of 140 normal human eyes. Relaxation of the extraocular muscles together with an increase in the coefficient of facility of outflow appeared to be responsible for the decrease of intraocular pressure.

Paralyzing the extraocular muscles by intravenous injection of curare caused less of a decrease of the intraocular pressure than that produced by general anesthesia. Tonography showed a reduction of the rate of flow of aqueous together with a moderate lowering of the coefficient of facility of outflow.

Dr. G. Kallner, Chief, Health Section, Central Bureau of Statistics of the Government of Israel, made the statistical calculations.

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The Lens in Congenital Galactosemia

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Congenital galactosemia is now well established as a hereditary disease caused by an inborn error of galactose metabolism. The clinical features of this rare condition are manifest very early in life, and their relationship to the ingestion of galactose has been amply documented.[1-5] The main features consist of early nutritional failure hepatic and splenic enlargement, jaundice, lethargy, osteoporosis, mental retardation, and cataract formation. The latter two signs usually occur at or about the fourth week of life. The cataracts that have been noted in the literature have varied in appearance from a ring-like lamellar opacity, with or without vacuoles in the anterior cortex, to zonular and nuclear opacities.[3,5-11] This varied picture is probably related to the severity and duration of the galactosemia and to the age of the patient.

Mitchell [12,13] and Day [14] reported on the occurrence of experimental cataracts in rats fed a high-galactose diet. The earliest histological appearance of such cataracts consists of hydropic changes in a few subcapsular lens fibers located at the equator. As opacification proceeds, an increasing number of fibers undergo vacuolation, and this process extends anteriorly to involve the anterior subcapsular cortex, later extending deeper into the cortex.[15] Many of the cataracts occurring in the human galactosemic patient present a similar slit-lamp and histological appearance. The basis for cataract formation in both the experimental animal and in the patient with congenital galactosemia is an increasing accumulation of galactose within the lens.

Fig. 1.—*A*, α-D-glucose; *B*, α-D-galactose.

Galactose is a six-carbon monosaccharide that differs from glucose only by virtue of the orientation of the hydroxyl group attached to the No. 4 carbon atom (Fig. 1).

Most of our dietary galactose is ingested in the form of lactose, which is a disaccharide present in milk. It consists of glucose and galactose joined together in a 1,4-glucose-β-galactoside linkage (Fig. 2).

In the intestine lactose is split into glucose and galactose. Galactose can then be utilized by the body in at least three ways. 1. Galactose is required for the synthesis of the galactolipids which constitute the great bulk of brain matter. This is not an absolute requirement, since these cerebrosides can also be synthesized from dietary glucose in the absence of galactose. 2. Galactose is incorporated into chondroitin sulfate, which, in conjugation with certain proteins, constitutes the glycoproteins found mainly in the ground substance (matrix) of cartilage and bone. 3. Most of the ingested galactose is converted into glucose and its derivatives and is thereby utilized by the body as an

Fig. 2.—Structural formula of lactose.

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important source of energy. It is in this pathway of galactose metabolism that the metabolic block occurs that leads to an accumulation of galactose-1-phosphate in certain body tissues.

Studies by Leloir,[16,17] Maxwell,[18] and Kalckar and his associates[19-22] have elucidated the manner whereby galactose is converted to glucose. Recently, Kalckar et al.[21,22] have succeeded in demonstrating the locus of the metabolic block which occurs in congenital galactosemia.

Scheme of Galactose Metabolism

Reaction 1 involves the phosphorylation of α-galactose to galactose-1-phosphate (gal-1-P):

$$\text{Galactose} + \text{ATP} \xrightarrow{\text{Galactokinase}} \text{gal-1-P} + \text{ADP}$$

Reactions 2 and 3 involve two specific nucleotides, uridine diphosphoglucose (UDPG) and uridine diphophosphogalactose (UDPgal), and two specific enzymes as shown below:

Reaction 2:

$$\text{gal-1-P} + \text{UDPG} \underset{\text{gal-1-P-uridyl transferase}}{\rightleftharpoons} \text{UDPgal} + \text{G-1-P}$$

Reaction 3:

$$\text{UDPgal} \underset{\text{UDPgal-4-epimerase}}{\rightleftharpoons} \text{UDPG}$$

Reaction 4:

$$\text{UDPG} + \text{PP}^{*} \underset{\text{DPN}}{\overset{\text{UDPG pyrophosphorylase}}{\rightleftharpoons}} \text{UTP} + \text{G-1-P}$$

In the red blood cell and liver in galactosemia there is an absolute or relative lack of the enzyme galactose-1-phosphate uridyl transferase[19-22] which is necessary in Reaction 2. This results in the marked accumulation of gal-1-P in these tissues, with the subsequent development of the clinical signs and symptoms characteristic of this disease. In the experimental animal fed a high-galactose diet, there is a similar accumulation of gal-1-P in the lens.

An opportunity to study the galactose metabolism in the lens occurred recently when a white boy, 4 weeks old, was admitted to Strong Memorial Hospital showing the typical picture of congenital galactosemia. This diagnosis was subsequently confirmed by laboratory studies. His lenses showed a slight degree of opacification localized to the anterior cortical region and extending towards the equator. These lenses were removed within one hour after death and assayed for gal-1-P uridyl transferase and UDPG pyrophosphorylase. Similar assays were carried out on several normal lenses. Thin slices from each lens were also subjected to the tetrazolium-formazan reaction,[23] which others have indicated to be a histochemical method designed to demonstrate the presence of succinic dehydrogenase.

Methods and Materials

All the lenses were removed under sterile conditions within one to two hours after death. A small portion of lens tissue was carefully removed and incubated with a 1% solution of 2,3,5-triphenyltetrazolium chloride (Eastman Chemicals) in 0.01 M phosphate buffer (pH, 7.2) for 30 minutes. The tissue was then fixed in 10% formalin.

The remaining major portion of lens tissue was quickly frozen and stored at -10 to -15 C for two to five days. This variation in the storage time did not affect the enzyme activities. Each lens was homogenized in 3 cc. N saline under cooling in an ice-water bath, and the insoluble protein fraction was removed by high-speed centrifugation. A 1 ml. aliquot from each sample was used for total protein determination by the micro-Kjeldahl method. The method of Kalckar et al.[24] was employed for gal-1-P uridyl transferase and UDPG pyrophosphorylase determinations.

* PP, inorganic pyrophosphate.

Duplicates were run for each assay, and the results varied within ±5%. Similar assays were done on red cell hemolysates derived from five normal persons, and the results agreed closely with those reported by Kalckar and his associates. The enzyme activities were calculated in micromoles of substrate (UDPG) consumed per gram of soluble lens protein in 1 ml. of homogenate. Since the amount of soluble lens protein per milliliter of homogenate was roughly one-twentieth of the concentration of hemoglobin expressed in grams per milliliter of hemolysate, the corresponding units of enzyme activity would be approximately 20 times higher for the normal lens as compared with the values derived for the normal erythrocytes.*

Results of Transferase and Pyrophosphorylase Assay

Table 1 shows the results obtained from assaying two galactosemic lenses (obtained from one patient) and two normal lenses. Table 2 shows the level of these two enzymes in the red cell hemolysate from five normal persons. The level of UDPG pyrophosphorylase activity was consistently higher in all the assays as compared with the values reported by Kalckar et al.[24] A lower range of activity similar to Kalckar's results (1.7-7.5 units) could be obtained by increasing the initial concentration of UDPG by approximately 20% to 25%.

* All the reagents for the gal-1-P uridyl transferase and UDPG pyrophosphorylase assays were obtained from the Sigma Chemical Company, St. Louis.

TABLE 1.—*Enzyme Activity in Galactosemic and Normal Lenses*

	Units of Gal-1-P Uridyl Transferase Activity *	Units of UDPG Pyrophosphorylase Activity *
Galactosemic lens No. 1	−0.68 (−0.034)†	391.73 (19.59)
Galactosemic lens No. 2	−0.47 (−0.024)	380.01 (19.00)
Normal Lens A	46.13 (2.36)	241.49 (12.06)
Normal Lens B	25.05 (1.25)	146.93 (7.35)

* The enzyme activity is expressed in micromoles of UDPG consumed per hour per gram of soluble lens protein per milliliter of homogenate.

† The values in parentheses are obtained by dividing the original value by 20 to arrive at a figure comparable for enzyme activity in the red blood cell.

TABLE 2.—*Enzyme Activity in Red Cell Hemolysate*

Subject	Age	Units of Gal-1-P Uridyl Transferase Activity *	Units of UDPG Pyrophosphorylase Activity *
A	4 wk.	2.45	48.00
B	10 mo.	2.06	31.32
C	28 yr.	5.84	42.21
D	30 yr.	4.82	44.42
E	22 yr.	3.20	38.60

* The enzyme activity is expressed in micromoles of UDPG consumed per hour per gram of hemoglobin per milliliter of hemolysate.

Results of Tetrazolium-Formazan Reaction

The tissue incubates from the two galactosemic lenses showed no reaction. Similar incubates from the two normal lenses developed a strong purplish-red color localized to the epithelial zone of the lens; this color was easily visualized grossly as well as microscopically.

Comment

The results of the transferase assay on the lens are definitive. While there was a complete lack of gal-1-P uridyl transferase activity in the galactosemic lenses, the units of activity obtained in the two normal lenses compared favorably with the values derived for normal erythrocytes in our experiment and with those reported by Kalckar et al.[24] As previously indicated, the expected level of transferase in the normal lens would be approximately 20 times the value derived for the red cell due to a 20-fold difference in concentration.

The level of UDPG pyrophosphorylase in the galactosemic lens is apparently elevated in comparison with the corresponding values for the normal lenses. This may or may not prove to be significant when more assays are performed on normal lenses.

Although the liver is probably the major site for converting galactose to glucose, both the red blood cell and lens are also capable

of performing this function. In the normal person it seems unlikely that galactose would be an important constituent in lens metabolism, since the ingested galactose is probably quickly converted to glucose by the liver before it could rise to any significant level in the lens. In the milk-fed infant the lens is probably called upon to handle galactose to a much greater extent than in later life. The absence of gal-1-P uridyl transferase in such a lens can therefore result in a very rapid accumulation of galactose-1-phosphate. In rats fed a high-galactose diet, Schwarz and Goldberg [25] found that this ester accumulates in the lens capsule. The mechanism whereby this high level of gal-1-P exerts its action has not been proven, but the assumption that the accumulation of this ester may lead to an inhibition of the oxidative metabolism of the lens epithelium is probably a valid one. This assumption is augmented by the results of the tetrazolium-formazan reaction on the galactosemic lens, which indicated a marked diminution of succinic dehydrogenase activity in the epithelium. A strong positive reaction resulting from the reduction of tetrazolium was noted in slices from both normal lenses. It would therefore seem that the oxidative metabolic cycle is seriously embarrassed in the galactosemic lens by the accumulation of galactose-1-phosphate. The energy required for protein synthesis will be markedly depleted, and this will result in an inhibition of the synthesis of protein. Dische et al.,[26] in their studies on experimental galactosemic cataract, have shown that the synthesis of soluble protein is markedly depressed and that this inhibition coincides closely with the beginning of galactose feeding.

It is also of interest to note that the mother of the infant affected by congenital galactosemia and his only sibling (male, aged 7) both showed a marked depression of erythrocyte transferase activity. The level in the mother was 0.8 units, and the brother showed an enzyme activity of 0.75 units. The mother also showed minimal lenticular opacities situated in the deeper layers of the anterior cortex; she had been aware of this condition since childhood. But the mother and brother were otherwise in good health, and their galactose-tolerance curves were normal. Both these persons, although they show a low level of transferase enzyme, apparently have a sufficient amount to enable them to metabolize galactose adequately. It is also possible that the body has a secondary pathway for metabolizing galactose, and it has been observed that as patients with galactosemia grow older they apparently develop an increased ability to metabolize galactose.[3] This additional pathway probably occurs via a pyrophosphorylase reaction similar to Reaction 4 previously described and involves the enzyme UDP galactose pyrophosphorylase.

$$\text{gal-1-P} + \text{UTP} \underset{\longleftarrow}{\overset{\text{UDPgal—pyrophosphorylase}}{\longrightarrow}} \text{UDPgal} + \text{PP}$$

Neufeld et al. have recently found such an enzyme in plants.[27] Another possibility is suggested by a report from Topper and Pesch [28] in which they found, with in vitro studies, that the steroids progesterone, methyltestosterone, hydrocortisone, and cortisone all exert a profound stimulatory effect on galactose oxidation; this effect occurs somewhere between cell entry and conversion to glucose-6-phosphate.

From the preceding discussion, it is apparent that further investigations are necessary to determine the exact mechanism involved in the development of galactosemic cataracts. With present-day micromethods, a thorough analysis of the amino acids forming the protein fraction that is apparently involved is now feasible. Similar analyses in the experimental animal may also prove useful. Once this is accomplished, the information gained will not only be of value in this rather rare condition but also will in all likelihood shed a good deal of light on the general problem of cataractogenesis.

Summary

The lens in congenital galactosemia is lacking in the enzyme galactose-1-phosphate

uridyl transferase. The normal lens does show galactose-1-phosphate uridyl transferase activity in amounts corresponding to the levels found in the normal red blood cell. The oxidative metabolism of the lens epithelium in congenital galactosemia appears to be markedly impaired. Alternative pathways of galactose metabolism are considered.

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Retinitis Punctata Albescens

A Functional and Diagnostic Evaluation

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Introduction

Retinitis punctata albescens is a tapetoretinal disorder characterized by an ophthalscopic picture of diffusely scattered white, dot-like lesions situated deep to the retinal vessels and associated with some impairment of night vision.* It is usually congenital or commences at an early age; the frequent occurrence of parental consanguinity suggests a recessive mode of inheritance. Pallor of the optic disc, reduction in caliber of the retinal vessels, and pigment deposition, either interspersed among the white spots or forming their core, are frequently reported. Functional manifestations may include decreased visual acuity, constriction of visual field, and alterations in color perception. The condition is usually stationary or very slowly progressive, but in some cases it may run a degenerative course similar to that of retinitis pigmentosa.

In a critical review of the literature in 1910, Lauber [3] selected more than 25 cases of "so-called retinitis punctata albescens" and placed them in a separate category on the basis of their stationary and functionally mild character. Common to most of these cases were fundus lesions similar to retinitis punctata albescens only in the appearance and distribution of the punctate white areas; concomitant signs of pigmentation, vascular constriction, and atrophic disc changes were invariably absent. Functional deficiencies, when present, were of less severity: only nyctalopia was consistently reported. It was to this essentially stable and relatively unaffected group that Lauber applied the term fundus albipunctatus cum hemeralopia congenita, reserving retinitis punctata albescens for the degenerative forms with unfavorable visual prognosis. Although there appeared to be transitional forms between these two extremes, the introduction of this new terminology implied the possible existence of differences other than the destructive potential of the disease. Others, however, prefer to disregard this differentiation and consider the nonprogressive form as the stationary expression of retinitis punctata albescens.[4]

In the present study clinical, psychophysical, and electrophysiological techniques have been employed in the examination of five members of a family in which two of the male siblings displayed the punctate white fundus lesions suggestive of retinitis punctata albescens. The diagnostic and prognostic implications of the findings are discussed.

Report of Cases

The family under consideration, of Puerto Rican origin, comprises the following members: father (age 61), mother (age 51), four sons (from 14 to 24 years of age), and a 21-year-old daughter. The parents are third cousins.

Positive ophthalmoscopic findings were present only in Brothers A (age 19) and B (age 14). Peripheral to the disc and macular regions the fundi were studded with a multiplicity of discrete white dots situated

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*A good general description of this condition may be found in Duke-Elder [1] and in Elwyn.[2]

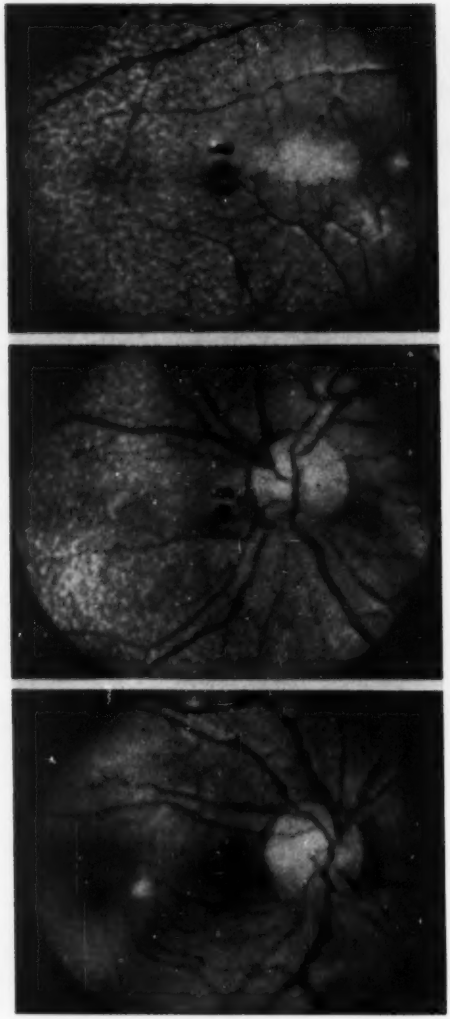

Figure 1

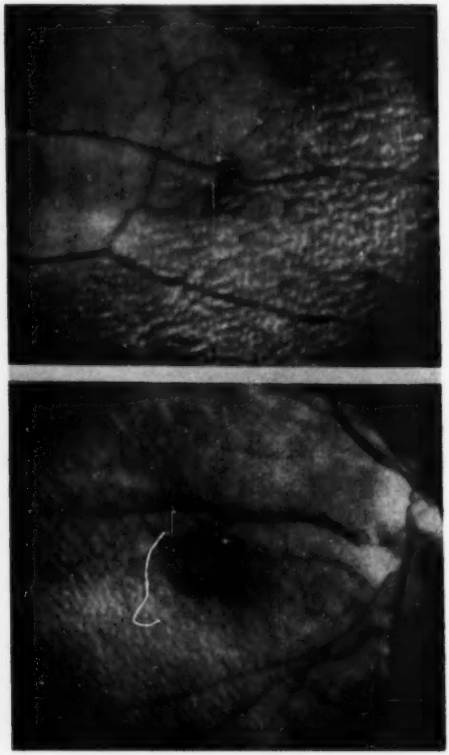

Figure 2

Fig. 1.—Fundus photographs of Brother A. Upper, temporal to macula, right eye. Middle, nasal retina, left eye. Lower, disc and macula, right eye. Note confluence of punctate lesions toward the periphery, with sparing of the disc and macular regions.

Fig. 2.—Fundus photographs of Brother B. Upper, temporal to macula, left eye. Lower, nasal to disc, left eye. The similarity in caliber and distribution of the punctate lesions to those of Brother A may be seen.

deep to the retinal vasculature. The almost identical form and distribution of the fundus involvement in the two brothers is shown in Figures 1 and 2. These punctate lesions were, for the most part, no larger than the diameter of a second-branch arteriole, but they tended to enlarge and coalesce into bacillar, spirillar, or dumbell forms as they approached the periphery. Fundus study of the rest of the family was negative, except for the presence of a few scattered drusen in both eyes of the mother, associated with a posterior subcapsular cataract in the left eye. The mother's serology was positive.

It is significant that the fundus pathology present in the two siblings was not associated with visual symptoms or any history suggestive of night blindness.

Apparatus and Procedure

The mother and four sons underwent a complete ocular examination. This included,

in addition to ophthalmoscopy and biomicroscopy, the testing of central visual acuity, color discrimination (Hardy-Rand-Rittler pseudoisochromatic plates with Macbeth illuminant C), tangent screen examination at 1 meter under 7 ft-c. illumination (targets: 0.5 mm., 3 mm. white, and 3 mm. blue), peripheral field determination on the A. O. Brombach perimeter (3 mm. white target), dark adaptometry, and electroretinography. The latter two procedures are described in further detail.

The course of dark adaptation was determined with the Goldmann adaptometer following an initial 10-minute exposure to 350 millilamberts of full-field luminance in

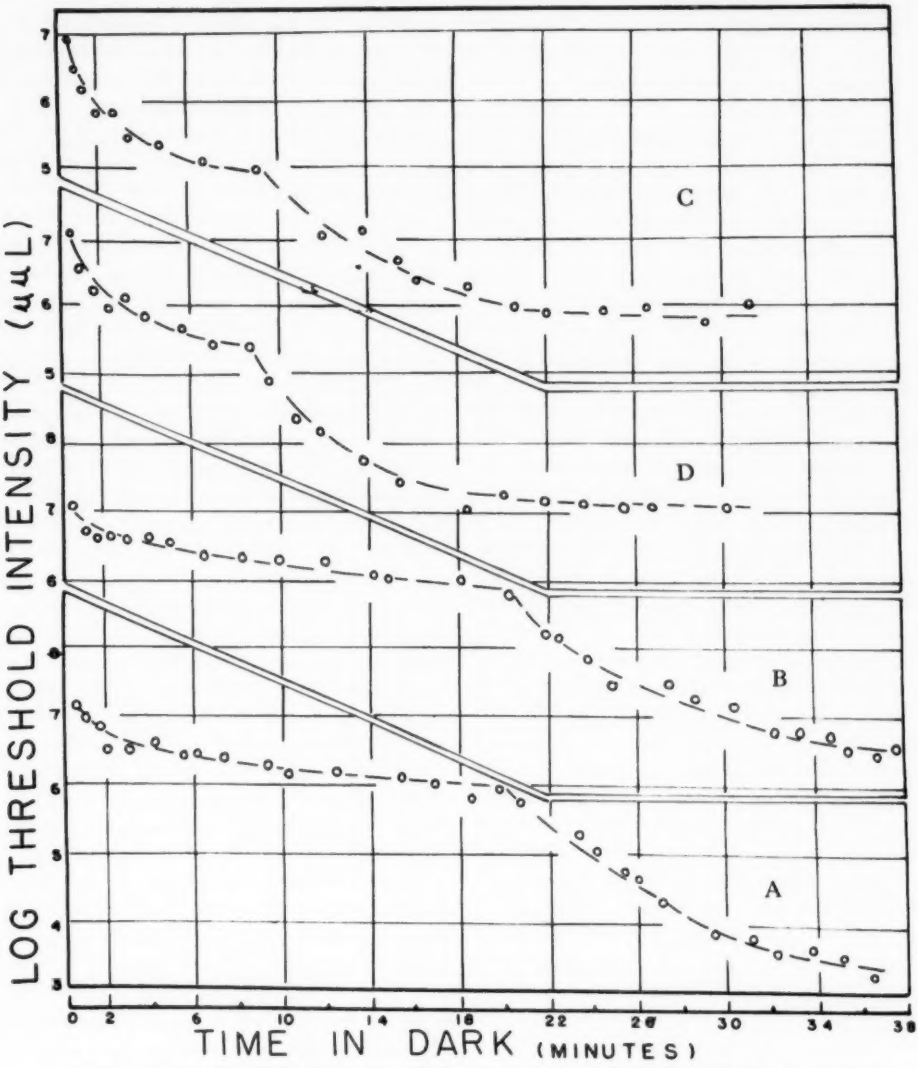

Fig. 3.—The dark-adaptation curves of the two unaffected Brothers (*C* and *D*) are presented for comparison with those of the affected two (*B* and *A*). Note the elevation of thresholds throughout the prolonged primary segment and the delay in onset of scotopic function in the latter two cases.

the integrating sphere of the instrument. White light was employed for both preadapting and test fields; the latter subtended 6 degrees at the patient's eye, with its center 11 degrees below the red fixation point. All thresholds were obtained in an ascending series, the intensity of the test patch being raised from a subliminal level by reducing the density of the neutral tint wedge. Periodic test exposures were of 0.5 second duration. Natural pupil and monocular observation were used throughout.

Electroretinograms (ERG's) were recorded with a Burian-Allen contact lens electrode led from the right cornea following instillation of 0.5% tetracaine (Pontocaine) and 1% methylcellulose. Amplification and recording were made by capacitance coupling (time constant at 0.2 second) to one channel of an Offner ink-writing electroencephalograph (Model D) operating at a paper speed of 60 mm. per second. The light source was a Grass Photostimulator (Model PS-1) set into an opaque cylinder, illuminating a ground glass diffusing surface subtending 25 degrees at the patient's eye. The light stimulus, approximately 10 microseconds in duration, was triggered manually by an electronic flasher, and its onset was recorded on a second channel of the EEG. Electroretinographic responses were elicited with stimuli of either 6×10^7 millilamberts (approximate) peak luminance (I_{max}) or reduced to 2% of this maximal value by interposition of a Wratten 1.7 neutral density filter ($I_{1.7}$).

ERG's were obtained under the following experimental conditions: The patient was adapted to the dim room illumination of 1.5 ft-c. (stimulus I_{max}); recording was done at preselected intervals during the course of dark adaptation following 6 minutes of light adaptation to 1834 millilamberts (stimulus $I_{1.7}$); recording was done after 40 minutes of dark adaptation (stimulus I_{max}).

Results

The results of all test procedures other than dark adaptometry and electroretinography were within normal limits for the five subjects examined. Data obtained for the mother were essentially normal and are not included in the following report.

In Figure 3 the dark-adaptation functions are shown, the upper pair of which (Brothers C and D) are typical examples of the normal configuration and threshold levels for the preadaptation conditions employed. The data for the two affected brothers (A and B) are sufficiently similar to be expressed by a single biphasic curve. For these subjects the increase in photopic sensitivity, following an initial drop in threshold, is extremely gradual and exaggerated by the delayed onset of scotopic function. In spite of the prolonged primary segment prior to the transition point, cone sensitivity remains subnormal. The delay in the appearance of rod adaptation is marked, occurring after approximately 20 minutes in the dark and proceeding rapidly thereafter to almost normal levels.

Illustrative examples of electroretinographic tracings for the various conditions of stimulation are shown in Figure 4. Electroretinograms recorded from the unaffected brothers indicate a steady rise in amplitude of both positive (b-wave) and negative (a-wave) components during the course of dark adaptation. Characteristic of the tracings for Brothers B and A are the poorly defined a-waves and the noticeable delay in the rise of positivity early in adaptation. Figure 5, in which the positive potential, as measured from the trough of the a-wave to maximum positivity, is plotted as a function of time in the dark, illustrates this retarded rate of development. Although the flash stimulus ($I_{1.7}$) was chosen to elicit scotopic components primarily,[5] some photopic contribution is probably present.† It should be noted that little difference exists between subjects when our routine clinical response indicators are utilized, i. e. maximum stimulation in dim room illumination and following complete dark adaptation.

† Despite this low-intensity stimulation, a small response (approximately 20μv.) was present at the flicker rate of 30 per second.

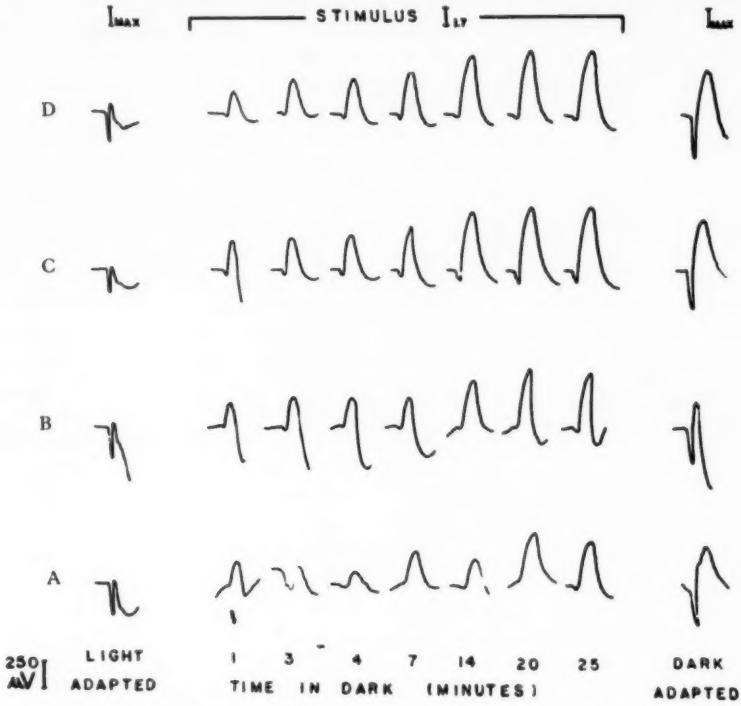

Fig. 4.—Electroretinograms obtained under various conditions of stimulation.

Comment

The two affected subjects in this study show the characteristic punctate white lesions of retinitis punctata albescens without the presence of pigmentation, narrowed vessels, or disc changes. Both cases demonstrate a mild impairment of scotopic function, not associated with symptoms of nyctalopia. This defect is reflected in the delayed appearance of the rod segment of the dark-adaptation curve, which subsequently reaches normal threshold levels. The reduced b-wave amplitudes of the ERG, found early in the course of dark adaptation, also suggests some scotopic deficiency. Since this depression is not marked, ERG evidence of a scotopic deficit is suggestive but not conclusive. The photopic mechanism appears to be relatively unimpaired. Visual acuity, color vision, central and peripheral visual fields, and the photopic ERG were essentially normal. However, the primary phase of the dark-adaptation curve, usually ascribed to cone function, reveals a decreased rate of development as well as elevation of threshold.

From the clinical standpoint, the significance of the functional studies of these two patients lies in the information that they may afford as to the eventual course of the retinopathy. This is of importance, since, as previously mentioned, retinitis punctata albescens may vary from a mild stationary deficit to a progressive degeneration. Unfortunately, the fundus picture alone is not an adequate guide to the clinician. Cases commencing with white spots and minimal symptoms have been known to develop the ophthalmoscopic and functional stigmata of retinitis pigmentosa and its variants.[6,7]

In correlating the results of adaptometric and electroretinographic studies in previous cases of retinitis punctata albescens with the stationary and progressive forms of the disease, patients will be classified according

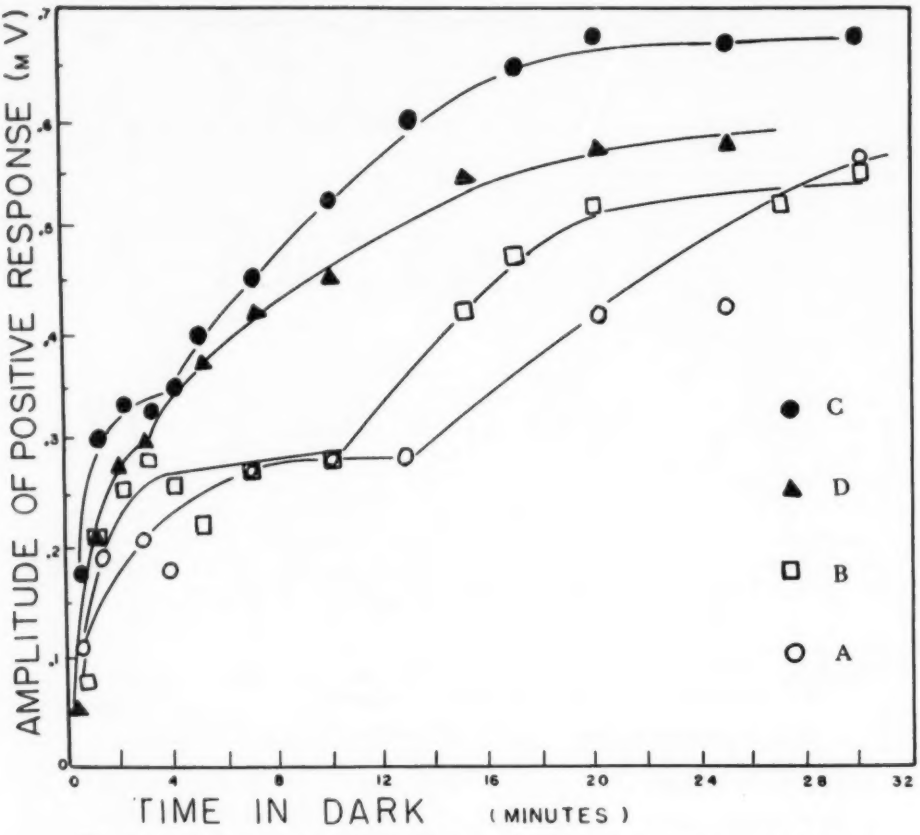

Fig. 5.—The influence of dark adaptation of the positive electroretinographic response. Positive potential is measured from the trough of the a-wave to maximum positivity.

to the criteria suggested by Lauber.‡ The term fundus albipunctatus will be applied to those cases with characteristic white spots below the level of the retinal vessels but without vascular involvement, optic pallor, or abnormal pigmentation and with normal or only slightly constricted visual fields. Cases classified as progressive will be those with some vascular attenuation, pigmentary or atrophic disc changes, and marked field constriction or ring scotomas. This distinction to a curve, which then paralleled the forms is somewhat arbitrary, since Lauber himself pointed out that intermediate forms exist.[3]

‡ This classification is not necessarily that originally used by the various reference authors.

Dark-adaptation curves, all differing significantly from the normal, have been reported in three patients with fundus albipunctatus. McDonald and Adler report a patient 44 years of age in whom dark adaptometry revealed a normal photopic segment followed by a rod portion which slowly adapted and reached in 30 minutes the level attained by the normal in 12 minutes.[8] In a 62-year-old man whose condition remained stationary over a 50-year period, Franceschetti and Chome-Bercioux found a prolonged (20-minute) and elevated cone segment followed by an abrupt transition between stationary and progressive scotopic segment of a normal subject in its rate of adaptation.[9] Franceschetti and

Dieterle subsequently reported a 57-year-old patient with fundus albipunctatus in whom only a cone threshold is measurable, with no transition to scotopic levels, a finding in sharp contrast to Franceschetti's first case.[10]

In the present investigation, the most dramatic departure from normal is similarly seen in the dark-adaptation functions of the affected brothers. Particularly striking is the almost normal rate at which scotopic sensitivity returns once the transition to rod function has occurred; it is almost as if a critical value of some catalytic component is required to trigger the events leading to photochemical regeneration. Owing to differences in adaptation and test conditions, the results of this experiment and those of other investigators may not be directly comparable. However, the anomalous functions appear very similar to those of Franceschetti's initial case, the author having stressed the protracted rate of "primary" adaptation.[9] Although the gross appearance of these curves differs from that of McDonald's and Adler's subject, the consequences would be almost the same, a prolonged temporal requirement before proper scotopic function is attained.[8] It should be noted that only our subjects remained essentially free of symptomatology relating to night vision.

It is apparent from the variable findings and the small number of cases that no generalizations can be drawn regarding the adaptometry functions in fundus albipunctatus. Furthermore, aberrations in dark adaptation, almost identical to those which we have found, have been seen in some of the 24 cases of cirrhosis of the liver reported by Patek and Haig, indicating that the punctate lesions may not be essential to the adaptometric defect.[11] In the absence of histological data as to the nature and location of the observable lesions, the extent to which they reflect the underlying pathology remains problematical.

François et al. have reported dark-adaptation curves in two cases of frankly progressive retinitis punctata albescens.[12] In one instance the curve was monophasic (absence of the scotopic portion), whereas the other case revealed a transition point within the first five minutes but both segments of the curve were abnormally elevated. On the other hand, Wilmer's patient, a 47-year-old man with the progressive form of the disease, is reported as another example of retarded scotopic adaptation with a normal final threshold.[13] Dark-adaptation functions have also been obtained from two young adults with the ophthalmoscopic signs of fundus albipunctatus but associated with marked concentric contraction of the visual field. The case of Franceschetti and Dieterle was reported as having a dark-adaptation curve only slightly better than that found in cases of retinitis pigmentosa.[14,15] Paradoxically, the subject studied by François et al., with a more severe limitation of the visual field, had a dark-adaptation curve with a normal "break" and final threshold, although there was some retardation in the rate of scotopic adaptation.[12] Although the latter two cases may represent transitional forms, we are again confronted with the extreme variability which prevents identifying retinitis punctata albescens with some unique adaptometric contour.

In 1954 Franceschetti reported normal ERG findings in his first case of fundus albipunctatus, the 62-year-old man mentioned previously.[14] The knowledge that the ERG is usually absent early in the course of such progressive tapetoretinal degenerations as retinitis pigmentosa led Franceschetti to suggest that the ERG may serve to distinguish between fundus albipunctatus and the early stages of progressive retinitis punctata albescens. Thus the author contends that the ERG profile is normal in fundus albipunctatus and subnormal or absent in the latter affliction. The ERG results reported by François for his two progressive cases of retinitis punctata albescens further support this distinction.[12] In one patient no electrical activity was elicited. The other showed a markedly depressed response in one eye and an extinguished ERG in the other. However, recent familial studies in dominant forms of retinitis pigmentosa have shown gradations in the ERG response from

moderate reduction to complete extinction, corresponding to the progressive stage of the disease.[16] It is possible, therefore, that the ERG responses in retinitis punctata albescens may similarly parallel the degenerative course of the retinopathy. Thus, a normal response in early cases does not preclude the possibility that we are dealing with a progressive degeneration. We cannot, therefore, concur in the use of a single metric for differentiation, particularly since normal ERG's have been reported in cases with widely differing characteristics, i. e., in a patient with moderate field constriction but with a dark-adaptation curve scarcely better than found in retinitis pigmentosa,[14,15] in another with severe constriction of field and a prolonged dark adaptation,[12] and in yet another in whom the fields were normal but who showed complete absence of a scotopic segment during dark adaptation and deuteranomaly.[10] Thus we are confronted with a broad spectrum of dysfunction associated with a normal ERG.

Although we have obtained essentially normal responses by our routine clinical procedure, reduced-amplitude tracings were obtained when the ERG was evoked during the course of dark adaptation. Along with irregularities in a-wave activity there is a delayed rise of positive potential, the response amplitude eventually reaching the lower limits set by the two unaffected brothers. The results suggest a physiological counterpart to the data of psychophysical adaptometry and demonstrate the value of appropriate variation in the experimental protocol.

Despite the variability in functional findings and lack of definitive criteria for differentiation, we may still assess the available evidence and speculate regarding the prognosis in our two affected subjects. The impression gained from the results of our test battery is that of a mild, functional, nondegenerative disorder, fundus albipunctatus. The findings satisfy those criteria which appear significant: a fundus with punctate white lesions, normal vasculature, and absence of pigmentation or signs of optic atrophy; normal visual fields and visual acuity, and a mild, nondebilitating scotopic deficit revealed by dark adaptometry and supported by changes in the electroretinogram. In addition, there is a striking similarity to the funduscopic, adaptometric, and electroretinographic findings in Franceschetti's 62-year-old patient, whose 40-year follow-up establishes him as the best documented case of fundus albipunctatus in the literature. It is hoped that we will have the opportunity to follow the course of this pathology and determine to what extent our findings remain unaltered.

The present study suggests an experimental approach which may be extended to the differentiation of various retinal degenerations and anomalies. The functional tests provide quantitative information which may be catalogued and compared with the results of subsequent examinations over a period of years.

Summary

Retinitis punctata albescens may vary from a progressive, degenerative disease to a stationary, asymptomatic variant, fundus albipunctatus, both of which may initially present an identical ophthalmoscopic appearance. The importance of differentiating the two varieties lies in the prognosis afforded the patient.

In the present paper, functional tests, including dark adaptometry and electroretinography, have been utilized in the examination of five members of a family, two of whom exhibited a multiplicity of punctate white fundus lesions deep to the retinal vasculature. The data were compared with the results of similar test procedures reported in the literature, and an attempt was made to determine whether any unique functional syndrome could be correlated with either the stationary or the progressive form of the disease. Considering the large number of intermediate stages which may exist, it was not surprising to find a wide variety of functional defects associated with either the degenerative or apparently stationary forms. However, in our subjects the relatively mild

ERG and dark-adaptometric defects, normal visual fields and acuity, and the absence of degenerative fundus signs suggest a diagnosis of fundus albipunctatus with favorable prognosis.

It has been emphasized, furthermore, that functional studies provide quantitative data which afford a means of following the degenerative course of a disease.

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Ocular Pressure in Experimental Cross Circulation

A Preliminary Report

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With the Technical Assistance of Miss Betty L. Hill

It has been observed since at least 1924 that the ocular pressure of one eye may be influenced by alterations in the pressure of the second eye.[1] The phrase "ophthalmotonic consensual reaction" has been used to describe this phenomenon.[1] The reaction has been studied in both humans and animals [2-4] and was recently characterized in some detail by Prijot and Stone,[5] who showed that in rabbits compression of one eye could elicit a fall in ocular pressure in the second, undisturbed, eye. This reduction was related to a decrease in aqueous flow while the facility of outflow remained relatively constant. The observation that systematically administered atropine blocked the consensual ophthalmotonic reaction suggested that the reaction was mediated, at least in part, by the autonomic nervous system.

Prijot and Stone [5] observed that the maximum effect of flow reduction upon ocular pressure occurred between 15 and 20 minutes after compression. This relatively long latent period does not seem altogether compatible with rapid nervous system transmission. The possibility that circulatory factors serve as mediators of the reaction is therefore proposed.

The purpose of the present study is to determine whether or not circulatory or humoral factors might play a role in ocular pressure changes induced by experimental compression.

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From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital, Baltimore. This work was presented in part at the Wilmer Resident's Association Meeting, March 28, 1958.

Method

Fifty-eight pigmented male rabbits,* weighing between 4½ and 7 lb., were maintained on a Sherwood Feed Pellet diet and water ad lib. All of the experiments were performed upon anesthetized animals. Paraldehyde, administered by gastric intubation, was used for anesthesia, and each animal received 0.7 cc. per pound of body weight diluted 1:7 in water. Paraldehyde was selected for anesthesia because it had been previously shown that stability of ocular pressure was best sustained with this type of anesthesia.[6] The animals were heparinized with 2 mg. per pound of body weight of aqueous heparin U. S. P.†

Ocular pressure determinations were made with a Mueller Electronic Tonometer, and the 1955 Friedenwald tonometric tables were used for calculation of ocular pressure.[7]

The animals were divided into four groups.

GROUP 1 (Cross Circulation).—Sixteen rabbits were used. The cross circulation of each pair was established by anastomosing the femoral vessels, that is, vein to artery and artery to vein (Fig. 1). The cannulation was performed with polyethylene tubing P. D. No. 160.‡ Three-way stopcocks were employed so that one opening led to a water manometer from which femoral arterial blood pressure recordings were made. After a stabilization period of not less than one hour, one eye of the first animal was compressed with a Baillart Ophthalmodyna-

* Research Supply Company, Philadelphia.
† Buffington's Inc., specific gravity 0.99.
‡ Intramedic, Adams.

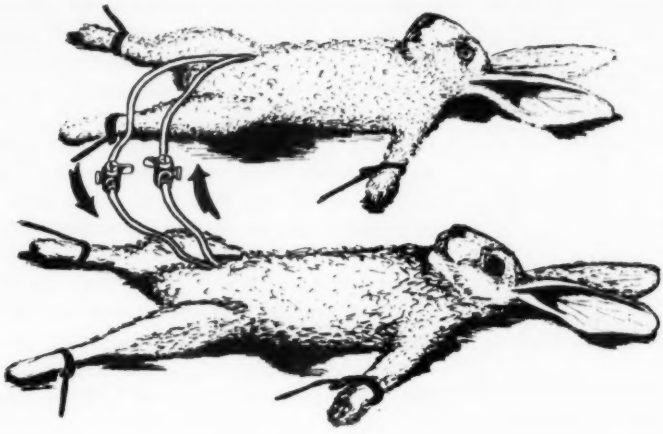

Fig. 1.—Schematic drawing of cross circulation experiment.

mometer adjusted to 100 gm. of pressure for four minutes, with the use of a modification of a procedure described in a previous publication.[5] Ocular pressure recordings were made on both eyes of the undisturbed animal at 2- to 3-minute intervals for a period of 45 minutes or longer after compression.

GROUP 2 (Cross Circulation Controls).—For control purposes, six animals were similarly studied in cross circulation; the ocular and blood pressures were followed for a period of two hours. These experiments were performed to determine whether cross circulation per se had any effect on ocular tension and to study the effect of repeated tonometric determinations on ocular tension.

GROUP 3 (Transfusion Experiments).—In this group, whole blood was obtained by cardiac puncture from 10 animals, the right eyes of which had been compressed in the same manner described for Group 1 above. The blood was collected during the period of three to eight minutes from the beginning of ocular compression. The blood obtained was injected intravenously into the test animals after the ocular pressures had been allowed to stabilize for not less than one hour following cannulation of one femoral vein. The average amount of blood injected was 5 cc. per pound of body weight. "Zero" time represents the beginning of transfusion. The transfusion itself was completed within six minutes. Ocular pressure recordings were made on both eyes of the

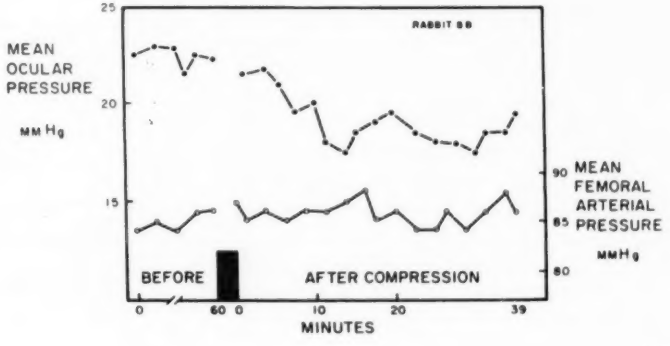

Fig. 2.—Representation of a typical cross circulation experiment.

TABLE 1.—*Cross Circulation—Mean Ocular Pressure in the Noncompressed Animal*

Animal	Precompression *	Minutes After Compression 0-10 *	11-20 *	21-45 *
1	30.7	25.0	21.7	—
2	15.1	10.2	10.8	—
3	21.3	21.6	20.8	19.8
4	15.3	16.3	14.6	14.5
5	21.2	19.2	17.6	18.8
6	10.9	11.3	9.5	9.1
7	20.3	16.5	14.1	14.7
8	22.4	20.6	15.6	16.6
Mean	19.7	17.6	16.7	15.5

* Figures indicate mean for each animal, given in mm. Hg.

recipient animal at 2- to 3-minute intervals for a period of not less than 30 minutes.

GROUP 4 (Control Transfusion).—In this group, six animals were studied in exactly the same manner as described above for Group 3, with the exception that these animals received whole blood from undisturbed animals, i. e., animals on which no ocular compression was performed. The main purpose of this series of experiments was to determine the effect of blood volume and hemodynamic changes upon ocular pressure.

Results

GROUP 1 (Cross Circulation).—Figure 2 illustrates a typical cross circulation experiment. The upper tracing indicates the mean ocular pressure values of both eyes. The lower tracing indicates the values for mean femoral arterial blood pressure obtained from the undisturbed animal. It will be noted that the ocular pressures of the undisturbed animal began to drop five minutes after the end of compression of the first animal. The greatest ocular pressure reduction occurred during the second 10-minute period after compression. Toward the end of the experiment, ocular pressure returned to the precompression levels.

The data for animals of Group 1 are presented in Table 1. The values recorded are the mean obtained from both eyes of the second, or noncompressed, animals. The time periods, 0 to 10, 11 to 20, and 21 to 45 minutes, were arbitrarily chosen for the purposes of statistical comparison of ocular tension in the same eyes before and after compression. The values recorded represent mean ocular tensions for the periods designated. Each of the values recorded are based on two- to three-minute interval determinations. Each determination was an average of not less than three ocular determinations taken at five-second intervals on each eye. The values presented in Tables 1 and 2 and in Figure 3 thus represent between 25 and 35 individual tonometric determinations.

The over-all mean value for each of the four periods described is given at the bottom of Table 1. These four values were used for graphic illlustration in Figure 3, and they represent the over-all mean ocular pressure changes in the undisturbed, or noncompressed, animals before and after ocular compression of the paired cross circulated animals.

It can be seen that the ocular pressure of the noncompressed animals fell after compression. The greatest fall occurred in the second and third 10-minute periods. Table 2 shows a statistical comparison of the pre- and postcompression tensions based on mean difference values between the same eyes for the periods indicated. The value for mean difference was calculated in the following way: For each animal, the mean difference between Periods 1 and 2, 1 and 3, and 1 and 4, respectively, were calculated from the data presented in Table 1. The mean of these differences is the value which is represented in Table 2. It can be seen

TABLE 2.—*Cross Circulation—Comparison of Mean Ocular Pressures Before and After Compression (Eight Animals)*

Period		Mean Difference, mm. Hg.	S. E.	n	P
I	Precompression & 0-10 min.	—1.67	±0.81	8	<0.10
II	Precompression & 11-20 min.	—4.06	±1.10	8	<0.01
III	Precompression & 21-45 min.	—2.98	±0.89	6	<0.04

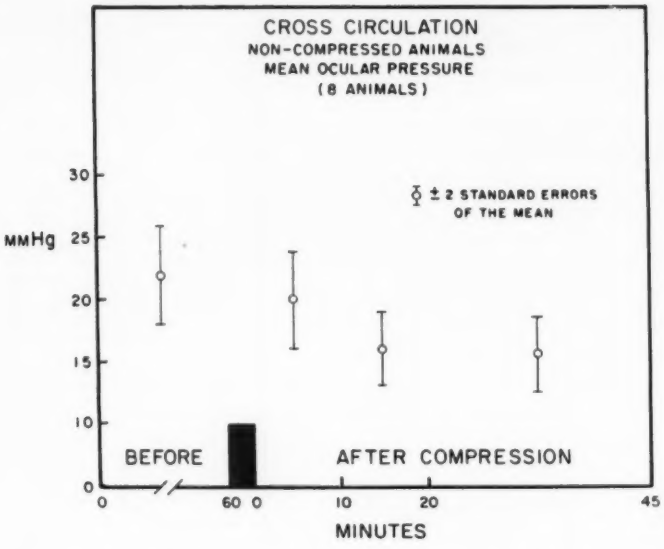

Fig. 3.—Graphic presentation of mean ocular pressure changes in noncompressed animals before and after compression in paired animal.

from the values for mean differences listed in this Table that a reduction of ocular pressure occurred in each of the three periods following compression. Although a reduction in pressure was noted in all three periods, only the fall in pressure in the second and third periods was statistically significant.

GROUP 2 (Cross Circulation Controls).—Figure 4 illustrates the mean ocular pressures obtained in three pairs of cross circulated animals on which no ocular compression was performed. Systemic blood pressures and ocular pressures remained stable during the period studied. Further control experiments will be discussed below.

GROUP 3 (Transfusion Experiments).—The mean ocular pressures obtained from animals in this group are listed in Table 3. The values recorded represent the mean of both eyes of the recipient animals. The time periods were arbitrarily chosen as for Group 1 above. The over-all mean value for each of the four periods is given at the bottom of Table 3. These four values were used for graphic illustration in Figure 5;

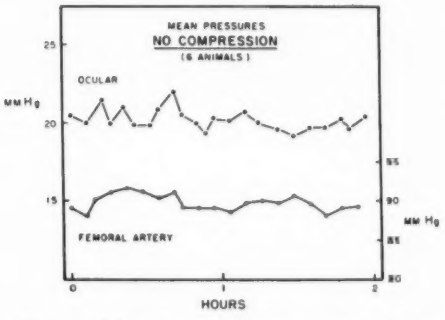

Fig. 4.—Mean ocular pressures obtained from three pairs of cross circulated noncompressed animals.

TABLE 3.—*Transfusion Experiments—Ocular Pressure in Animals Receiving Transfusion of Blood from "Compressed" Animals*

Animal	Pretransfusion *	Minutes After Transfusion 0-9 *	10-19 *	20-45 *
9	21.5 *	18.2	21.4	26.9
10	16.8	8.8	5.5	15.5
11	25.9	22.1	19.2	35.0
12	18.8	12.9	15.7	16.4
13	16.5	17.3	16.6	17.9
14	21.7	23.2	20.9	22.6
15	28.4	26.4	25.7	22.4
16	24.1	17.8	16.9	19.4
17	25.8	20.2	27.4	28.6
18	21.0	23.8	28.7	25.3
Mean	22.1	19.1	19.8	23.0

* Figures indicate mean for each animal, given in mm. Hg.

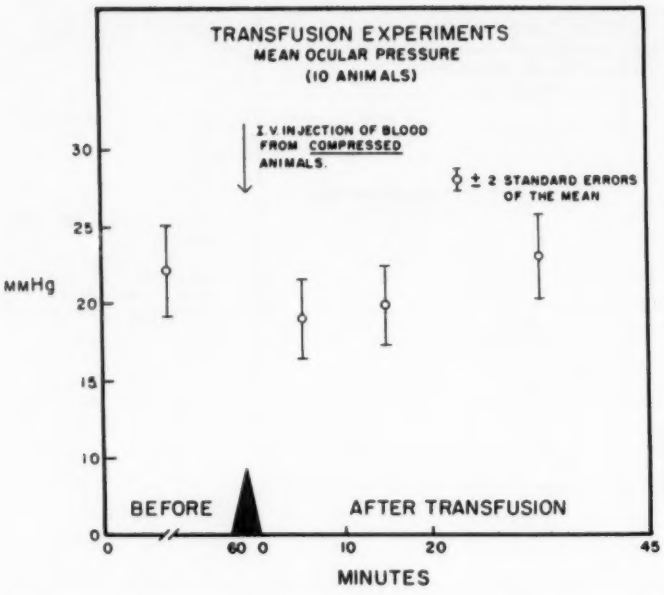

Fig. 5.—Graphic presentation of mean ocular pressure changes in noncompressed animals before and after transfusion from compressed animals.

they represent the over-all mean ocular pressure changes in the recipient animals before and after transfusion of blood obtained from animals, the right eye of which had been compressed. It can be seen from both Table 3 and Figure 5 that the greatest fall in ocular pressure occurred in the first post-transfusion period. Table 4 represents the statistical comparison for these periods following the same procedure employed for the data described above in compiling Table 2 (Group 1). It can be seen that no statistically significant fall in ocular pressure occurred in this group except in the first post-transfusion period.

TABLE 4.—*Transfusion Experiments—Comparison of Mean Ocular Pressures Before and After Transfusion of Blood from "Compressed" Animals (Ten Animals)*

Period		Mean Difference, mm. Hg.	S. E.	*P*
I	Pretransfusion & 0-9 min.	−2.98	±1.06	<0.04
II	Pretransfusion & 10-19 min.	−2.25	±1.68	N. S.
III	Pretransfusion & 20-45 min.	+0.98	±1.11	N. S.

GROUP 4 (Transfusion Controls).—Table 5 shows mean ocular pressures obtained in the control transfusion experiments in which recipient animals received donor blood from undisturbed animals. As can be seen from Table 6 and Figure 6, no statistically significant pressure changes occurred in the post-transfusion periods.

Comment

The data for ocular pressure changes obtained in these preliminary studies should be considered in terms of a relative decrease in pressure. The important observation is

TABLE 5.—*Control Transfusion Experiments—Ocular Pressure in Animal: Receiving Transfusion of Blood from "Noncompressed" Animals*

Animal	Pretransfusion *	Minutes After Transfusion 0-9 *	10-19 *	20-45 *
19	29.9 *	31.7	34.7	30.8
20	18.2	20.7	22.8	21.7
21	20.6	24.9	23.9	24.0
22	21.3	23.2	21.9	24.1
23	28.0	22.2	20.9	18.4
24	20.6	18.6	17.7	15.7
Mean	23.1	23.6	23.7	22.5

* Figures indicate mean for each animal, given in mm. Hg.

TABLE 6.—*Control Transfusion Experiments—Comparison of Mean Ocular Pressures Before and After Transfusion of Blood from "Noncompressed" Animals (Six Animals)*

Period		Mean Difference, mm. Hg.	S. E.	P
I	Pretransfusion & 0–9 min.	+0.45	±1.51	N. S.
II	Pretransfusion & 10–19 min.	+0.55	±1.93	N. S.
III	Pretransfusion & 20–45 min.	−0.65	±2.01	N. S.

that a reduction in ocular pressure occurred, and little emphasis should be given to the absolute values.

The greatest reduction of ocular pressure in the undisturbed cross circulated animals occurred in the second 10-minute period after compression (Table 2). It is interesting to compare these findings with those of Prijot and Stone,[5] who showed that the greatest reduction of ocular pressure in the ophthalmotonic consensual reaction occurred after a latent period of 15 to 20 minutes.

Further evidence for a circulating factor derives from the series of animals which received a transfusion of blood from animals whose right eye had been compressed, but which were not cross circulated. In this series, the maximum reduction of pressure occurred in the first 10 minutes after transfusion (Table 4).

It is interesting to speculate on the different latent periods noted in the cross circulation and transfusion groups. If a circulating substance is present which is responsible for the effect noted, one would expect a shorter latent period in the group of animals receiving a transfusion, since the time required for elaboration and accumulation of a humoral material is virtually eliminated by the experimental set-up. The substance is already present in the transfusing syringe. The dilution of the circulating material in the large volume of the cross circulating system might be a second factor which could lengthen the latency period in the group of cross circulated animals.

Two main controls were used for the ocular pressure changes: The first was a comparison of the same eyes before and after compression or transfusion, and the

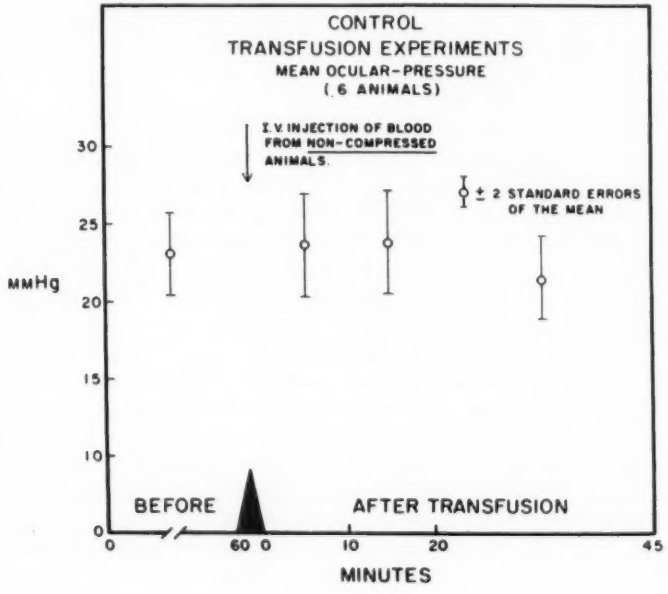

Fig. 6.—Graphic presentation of mean ocular pressure changes in animals before and after transfusion from noncompressed animals.

second was a small series of cross circulated animals in which only repeated tonometric determinations were made without any compression.

What of hemodynamic changes? Hemodynamic considerations might argue against the conclusion that circulatory factors are responsible for the ocular pressure reduction observed. It could be said that the injection of a relatively large blood volume, 5 cc. per pound of body weight, into a relatively small animal could cause a fall in ocular pressure on a hemodynamic basis. That this is apparently not the case is shown by the animals in Group 4 (Fig. 6), in which the ocular pressure remained stable after a transfusion of blood from undisturbed animals. Further, it may be stated that the blood pressure in the cross circulated animals remained stable and that blood pressure changes in the transfusion experiments both in controls and test animals revealed only a slight increase of mean femoral arterial blood pressure shortly after the beginning of the transfusion. This slight increase did not effect any reduction in ocular pressure. The effect of intravenously injected blood or fluids on aqueous dynamics in rabbits will be treated more fully in a separate publication.[8]

Another physiologic consideration is the question of the weight employed for ocular compression. It is apparent that 100 gm. of pressure is a considerable force; however, in these preliminary experiments, the sole purpose was to determine whether or not *any* cross circulating effect could be demonstrated following compression. Further quantitation of this stimulus in a more physiologic range is in progress.

Assuming the existence of a circulating factor responsible for the ocular pressure effects noted in these experiments, two as yet unsolved problems arise: First, where does such a factor exert its effect? Second, where is it elaborated? The first question has direct bearing on aqueous dynamics. The pressure-lowering effect of a humoral substance might be to reduce aqueous inflow or to increase the facility of outflow or both. The effect of flow reduction, for example, could be related to altered ciliary epithelial function. There are indeed several well-known physiologic conditions in which humoral influences act directly on the secretory and absorptive powers of epithelial cells, e. g., the effect of the antidiuretic hormone on the distal renal tubules [9] or that of secretin on the pancreatic cells.[10] A similar effect might be postulated for ciliary epithelium.

With regard to the site of elaboration of a circulating substance, it is of interest to note that some investigators have found humoral substances in the spinal fluid which have a pressure-lowering effect on the eye.[11] In addition, Becker and Christensen [12] have published results of the effect of vasopressin on ocular tension. These authors have shown that in man and in rabbits this substance produces a decrease of ocular tension. Here again, there appears to be a relatively long latent period of about 15 to 45 minutes.

It is obvious that the present study does not eliminate neurogenic components in either the consensual ophthalmotonic reaction in one animal or the ocular pressure-lowering effect in cross circulated animals. It is likely that both neurogenic and humoral elements play a role in both these reactions.

Summary

Preliminary data suggest that in rabbits there is a circulatory or humoral factor which can elicit a reduction of ocular pressure in an undisturbed eye after compression of another eye. This has been demonstrated both in cross circulated animals and in transfusion experiments.

The above observations indicate, but as yet do not prove, that hemodynamic factors are not responsible for the ocular pressure changes observed in this study.

Finally, we wish to caution against any premature conclusions concerning the presence of similar circulatory factors in human ocular disease or even under ordinary physiological conditions.

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Scleral Imbrication for Retinal Detachment

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It is my purpose to describe an improved type of scleroplasty. It has been developed at the University of Oregon Medical School during the past decade for the treatment of those types of retinal detachment which ordinarily do not respond to conventional transcleral diathermy. This operation has been named scleral imbrication, because the outer layers of the sclera are undermined and then overlapped in one or more quadrants of the globe. The technique was described briefly at the 1953 meeting of the Section of Ophthalmology of the American Medical Association.[1] Since that time others have recognized the scleral imbrication.[2,3]

As compared with other types of lamellar scleroplasty, scleral imbrication has several advantages. In the course of the procedure, the deeper layers of the sclera are exposed over a wide area. This permits accurate localization of retinal breaks before any diathermy is applied. This is possible because the choroid and remaining thin layer of sclera can be focally indented with forceps during ophthalmoscopic observation. Exposure also facilitates application of intense diathermy to these structures in the region of the retinal break with a minimal amount of scleral and vitreous damage. Then, after release of subretinal fluid, overlapping of the outer scleral layers produces profound flattening of the curvature of the globe, reduces its volume, and increases its rigidity in the region of the retinal break. Unlike other types of scleroplasty which may weaken the sclera, scleral imbrication actually strengthens the coats. The risk of wound separation during the healing period is less than with the other types of scleroplasty because a double row of sutures is used. Finally, the indentation of the deeper layers of the sclera and choroid induced by imbrication of the outer scleral layers favors good apposition of the pigmented epithelium with separated retina.

The scleral imbrication operation with various modifications has been in use at the University of Oregon Medical School since 1948. It has been applied in more than 100 eyes with a diversity of anatomical structures and types of retinal detachment. Although many of these eyes have been considered to have a poor prognosis, the operative procedure has been successful as a primary procedure in nearly four-fifths of all cases. This series includes cases operated on by the resident staff and cases of aphakic as well as phakic eyes. The follow-up period has been from 4 months to 10 years.

The individual members of the University of Oregon faculty have some differences of opinion relative to the indications for scleroplasty, but, in general, simple scleral diathermy, with or without release of subretinal fluid, is undertaken only in those eyes where there is a complete or nearly complete settling of the retina preoperatively. Even then, the scleral imbrication technique generally is applied whenever a large retinal break is present. This is done because the excellent exposure of the deeper layers of the sclera and choroid provided by this operation permits the accurate and intense application of diathermy in and around the retinal defect, as well as improved apposition of the separated retina with the pigmented epithelium.

A permanent flattening of the sclera in the region of the imbrication generally has been found in eyes which have been reoperated on (Fig. 1). For this reason, im-

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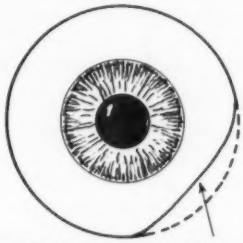
From the Department of Ophthalmology, The University of Oregon Medical School.



Marked flattening of globe obtained in inferior temporal quadrant by scleral imbrication.

Figure 1

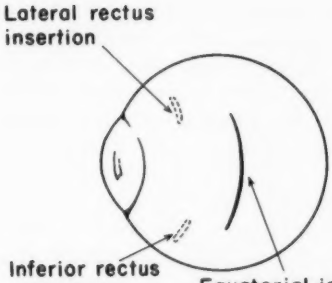
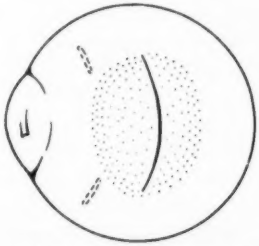


Figure 2

plants of polyethylene or other materials seldom have been indicated; however, such implants can be placed between the overlapped outer layers of the sclera and the infolded deeper layers of the sclera and choroid.

The technique of performing the scleral imbrication operation now will be described as it would be applied to a retinal disinsertion localized to one quadrant.* In the operation illustrated by the diagrams a disinsertion had occurred in the inferior temporal quadrant of one eye, but in this patient a bullous separation of the retina involved all but the superior nasal quadrant. In this instance, the patient's retina remained elevated in spite of binocular dressings and bed rest; therefore, it seemed essential to flatten the globe in the region of the break so that apposition could be obtained between the edges of the disinserted retina and the underlying pigment epithelium. Also, it was evident that a widespread and intense heat injury would have to be induced in the choroid in order to close the large retinal break.

The application of scleral imbrication to this type of retinal separation is as follows: The inferior nasal quadrant and the temporal half of the globe are exposed by an incision through the conjunctiva and Tenon's capsule in the equatorial region. Traction sutures of heavy black silk are placed under the inferior and lateral rectus muscles. The scleroplasty is begun with a scleral incision which follows the curve of the globe at the equator. The incision is perpendicular to the surface and extends about three-fourths of the way through the sclera (Fig. 2). For a disinsertion confined to the inferior temporal quadrant, the incision should extend from the inferior border of the lateral rectus to the temporal border of the inferior rectus. Whenever possible, it is desirable to avoid placing an imbrication under the rectus muscles, particularly the superior and inferior rectus. The marked flattening of the globe achieved by this procedure invariably will result in the development of a deviation. The incision is then undermined anteriorly and posteriorly, exposing the deeper layers of the sclera and choroid over a zone extending from the ora serrata to well behind the equator (Fig. 3). At this stage, the posterior lip of the scleral wound



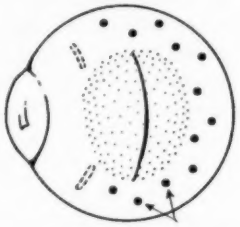
Incision undermined to expose deeper layers of sclera for diathermy

Figure 3

* This operation was illustrated by a movie presented at the Pacific Coast Oto-Ophthalmological Society at Vancouver, B. C., May 14, 1958, by Kenneth C. Swan and Paul Bailey Jr.

is grasped with forceps to control the globe while the interior of the eye is observed with the ophthalmoscope. The focal indentation of the thinned deeper layers of the sclera with the tip of the forceps permits accurate localization of defect in the retina without the need of preliminary placement of pins or diathermy. The next step, the application of diathermy, is begun only after the surgeon has assured himself that he has exposed the deeper layers of the sclera beyond the boundaries of the retinal defect.

The exposed deeper layers of the sclera are treated with multiple applications of a blunt-tipped electrode. To minimize heat injury to the vitreous and retina, a vacuum-



Focal areas of diathermy are applied through the sclera surrounding the area to be imbricated. The entire area under the scleral flaps is treated with diathermy applied with a blunt-tipped electrode.

Figure 4

tube-generated current of 5,000,000 cps is used with a sufficient intensity of current to produce the desired effect instantly.[4] This technique produces an intense heat injury in the choroid in and around the retinal break with minimal destruction to adjacent areas in the choroid or vitreous. The overlying outer layers of the sclera have been reflected and are undamaged.

A focal area of intense heat injury in the choroid is apt to be followed by later contraction, with resultant distortion of the surrounding tissues. A break in the retina in adjacent areas may result. To prevent this, it has been customary to surround any area of intense heat injury with a zone of focal diathermy-induced lesions. It is our custom to apply these focal diathermy-induced lesions posterior to the area of imbrication

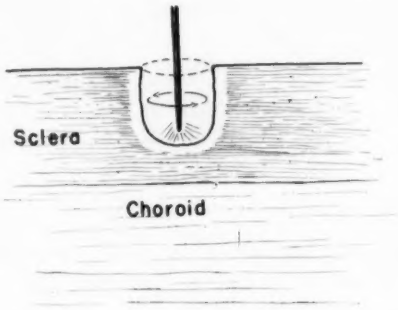


Figure 5

as well as the adjacent quadrants (Fig. 4). The usual technique is to use a partially penetrating needle type of electrode, which requires estimation of the scleral thickness and necessitates some scleral coagulation. At the University of Oregon a different technique has been developed. The deeper layers of the sclera and choroid are exposed in focal areas. An extremely fine needle of the type designed for electrolysis is used with a relatively high-amperage vacuum-tube-generated current. The needle tip is brought almost, but not quite, into contact with the tissues. The high concentration of current literally dissolves the sclera at the tip of the needle (Fig. 5). With this type of needle and an undamped constant current, it is possible to cut holes 1 to 1½ mm. wide in the surface layers of the sclera with little or no heat damage to the surrounding sclera. The holes are of proper depth when the color of the choroid becomes visible. A blunt-tipped electrode of 0.5 to 1 mm. in size is then applied to the base of these

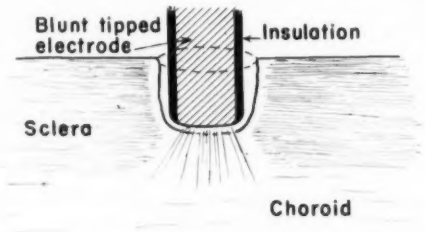
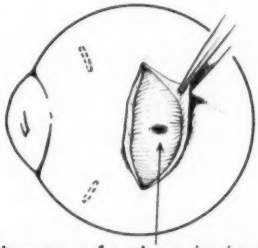


Figure 6

holes, and a low-amperage current is used to produce the focal areas of coagulation, which generally can be observed by ophthalmoscopy (Fig. 6). With this technique of cutting a hole in the surface layers of the sclera prior to the application of diathermy to the choroid, heat injuries to the sclera and vitreous are minimized and there is little risk of creating new holes in the retina, because the tip of the electrode is visible at all times.

Retinal fluid is released only after the dissection of the scleral flaps and the application of the diathermy are completed. This is important because applications of diathermy in the presence of a soft eye generally result in choroidal detachment. We

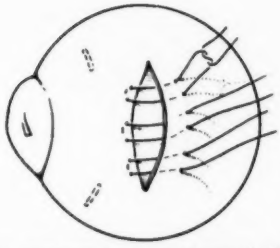


Deeper layers of sclera incised to expose choroid. Choroid carefully opened to release subretinal fluid.

Figure 7

have demonstrated that separation of the choroidal fibers occurs primarily in the outer layers. A high concentration of protein-rich fluid in these layers dissipates the current as well as the heat induced by it; thereby, a desirable degree of heat reaction in the choroid may not be obtained. In previous work in patients and animals, we have demonstrated that a choroidal detachment occurs in a high percentage of cases when the ocular tension is subnormal and the curvature of the sclera is altered by either surgery or heat shrinkage.[5]

In order to release subretinal fluid, a knife incision is made in the deeper layers of the sclera underneath the scleral flaps. A "draw" cut is made perpendicular to the limbus so as to parallel the major choroidal vessels (Fig. 7). The choroid generally can



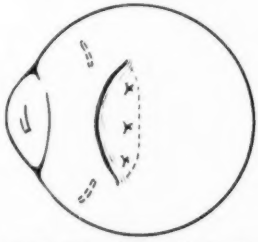
Mattress sutures are placed from under side of scleral flaps

Figure 8

be exposed without perforation by the knife blade; it can then be gently picked open either with the tip of the knife blade or with the needle, held parallel to the surface to decrease the risk of accidental perforation of the retina.

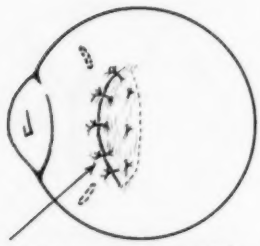
After the release of subretinal fluid, the area of choroid and sclera under the scleral flaps can be infolded or made to shrink by the application of a low-amperage current with a large ball type of electrode. This invariably produces a massive choroidal detachment in this area. At this stage, choroidal detachment is not detrimental and may even induce better apposition of retina and pigmented epithelium.

To produce the imbrication, two to four mattress sutures are placed through the anterior lip of the scleral flap from the underside (Fig. 8). These sutures are then passed through the posterior lip of the scleral flap from the underside and tied on



Mattress sutures, when tied, tuck the anterior flap under the posterior flap. Deeper layers of sclera and choroid are infolded.

Figure 9



Radial sutures are placed in anterior lip of posterior scleral flap.

Figure 10

the outside. Thereby, the anterior scleral flap is tucked under the posterior flap (Fig. 9). The forward edge of the posterior flap is then sutured to the sclera with a series of fine radial sutures (Fig. 10). Initially, silk was used with the scleral imbrication operation, but in the past two years 00000 and 000000 mild chromic absorbable surgical (gut) sutures have been found to be satisfactory. Also, we have in recent years closed the conjunctiva and Tenon's capsule with interrupted 000000 mild chromic gut sutures. In many cases the two layers are closed separately. Rapid healing of the external wound is obtained by this means with a minimum of reaction, and no sutures need be removed. Postoperative care of patients with scleral imbrication and diathermy is the same as in other types of surgery in the treatment of retinal detachment.

Summary

During the past decade an operation has been developed at the University of Oregon Medical School for the treatment of retinal detachment. The outer layers of the sclera are undermined and then overlapped to produce a marked flattening of the curvature of the globe in one or more quadrants. This operation has been designated as scleral imbrication.

As compared with other types of lamellar scleroplasty, scleral imbrication has several advantages. In the course of the procedure the deeper layers of the sclera are exposed over a wide area. Exposure permits accurate localization of retinal breaks before any diathermy is applied. This is possible because the choroid and remaining thin layer of sclera can be focally indented with forceps during ophthalmoscopic observation. Exposure also facilitates application of intense diathermy to the region of the retinal break with a minimal amount of scleral damage. Then, after release of subretinal fluid, overlapping of the outer scleral layers produces a permanent flattening of the curvature of the globe, reduces its volume, and increases its rigidity in the region of the retinal break. The deeper layers of the sclera, choroid, and pigmented epithelium beneath the imbrication are infolded with or without an implant. The operative procedure has been used in the treatment of more than 100 patients with various types of retinal detachment. It has been successful as a primary procedure in nearly four-fifths of these cases.

3181 S. W. Sam Jackson Park Rd. (1).

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Transplantation of the Lens

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It would seem that the lens is the ideal organ for transplantation because it is avascular and its antigen is contained in a membrane which probably does not allow protein molecules to pass. As long as the capsule is not damaged by the procedure, sensitization of the host is unlikely and consequently clear homo- and heterografts are to be expected unless the capsule itself sensitizes the host.

That the normal lens capsule is an effective barrier against the passage of larger molecules follows from the fact that the eye does not become sensitized to its own highly antigenic lens proteins except under pathological conditions. Further, sensitization of experimental animals with homologous or heterologous lens proteins failed to produce cataracts, even though lens antibodies were demonstrated in the anterior chamber.[1] Yet the capsule contains proteins and polysaccharides, and it therefore becomes a potential antigen when the lens is transplanted. If the antigenicity of the capsule is sufficiently strong, a subsequent immune response from the host may change its permeability. This could lead directly to cataract formation in the lens transplant, or lens proteins could leak through the capsule, sensitize the host, and indirectly affect the transparency of the graft.

For obvious reasons of metabolism and nutrition, the site of transplantation is the eye, and this will be the main topic of discussion, although the behavior of the lens auto- and homograft in subcutaneous tissue and in the peritoneal cavity will be dealt with briefly.

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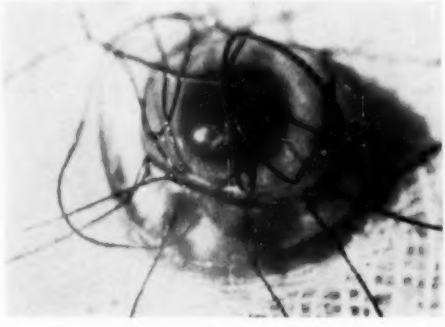
Transplantations to the eye may be expected to have the best chance when the original lens is replaced by the graft, but the procedure seemed to depend on overcoming certain technical difficulties. In preliminary experiments 20 homografts were performed in rabbits after extracapsular lens extractions. In all of these eyes the cornea turned completely cloudy and either the wound ruptured or glaucoma developed. Ten autografts underwent the same fate. Gradually a technique was developed in which small donor lenses were grafted to large recipient eyes, wound healing was sufficiently secured, and the donor lens was protected during the insertion by its own donor cornea. The preliminary experiments are not included in the results.

Lens Homografts

Method.—Albino rabbits, weighing between 8 and 12 lb., are anesthetized with pentobarbital (Nembutal) and ether and the hair around the eye is shaved. The rabbit is draped with a sterile sheet which contains a hole to expose the eye. The globe is luxated, and the luxation is maintained by pinching the center of the upper lid with a hemostat. A square of gauze containing a

Fig. 1.—Globe luxated, showing a groove and five preplaced silk sutures.



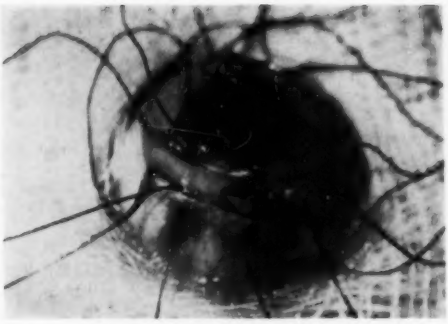


Fig. 2.—Anterior chamber opened and one large iridectomy performed.

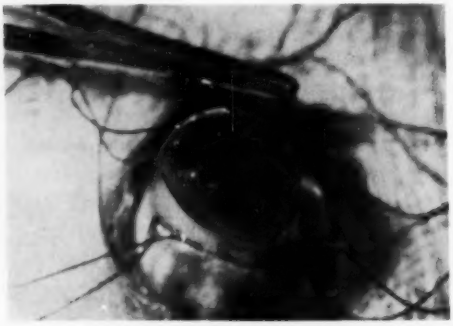


Fig. 3.—Extracapsular lens extraction.

hole is placed over the globe to eliminate any exposure of skin left by the sheet. The eye and the conjunctival sac are washed with a benzalkonium (zephiran) isotonic saline solution, and tetracaine (Pontocaine) is instilled if necessary.

A groove is made, with a Bard-Parker knife, on the corneal side of the limbus over the whole upper half of the eye, and five to six preplaced sutures are inserted. The anterior chamber is opened at 12 o'clock, and the opening is extended on both sides with scissors. One or two large iridectomies are performed at about 10 and 2 o'clock. The capsule is broken with forceps, and the lens is expressed, taking care to remove as much of the lens material as possible. If the donor lens is relatively large, approximately 0.1 to 0.2 cc. of vitreous is aspirated through the posterior capsule with a 20-gauge needle. The hemostat on the upper eyelid is removed to release most of the pressure on the globe, and the donor lens is inserted with the aid of a spoon-shaped instrument covered with donor cornea to prevent damage to the lens. When the lens is well in place under the iris, the spatula is gently withdrawn together with the protecting donor cornea and the sutures are tied. The globe is allowed to slip back into its proper position, if it has not already done so during the insertion of the lens. Chlortetracycline (Aureomycin) ointment is applied and sometimes di-isopropyl fluorophosphate (DFP). The lids are not sutured.

Preparation of Donor Lens.—Donor eyes were obtained from young albino rabbits, weighing approximately 5 lb. We were assured by the dealer that these rabbits were unrelated to the recipient animals.

After enucleation, the eye is rinsed with a benzalkonium-saline solution and wrapped

Fig. 4.—Transplantation of the donor lens into the recipient eye. Globe slips back during procedure.

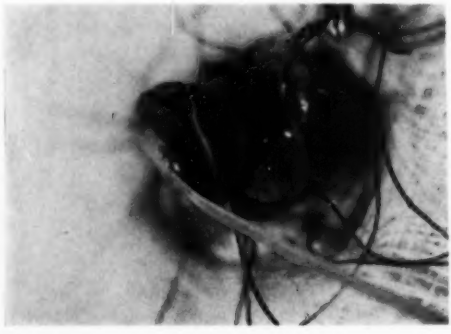


Fig. 5.—Sutures tied.

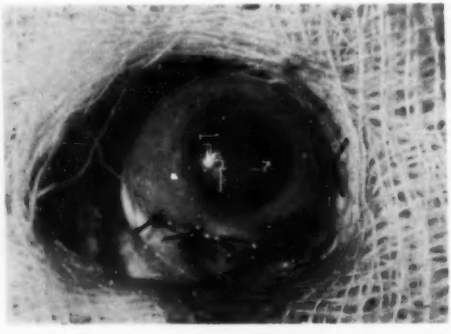


Fig. 6.—Re-formation of the anterior chamber.

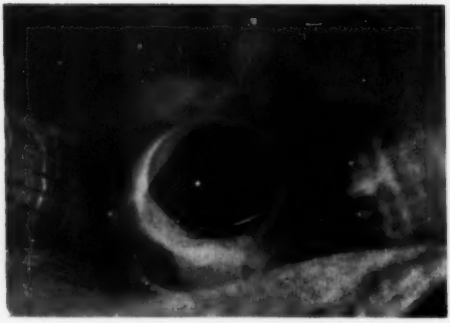


Fig. 7.—Donor eye. Cornea excised. Zonule fibers exposed.

in sterile gauze, and the anterior chamber is opened with a Bard-Parker knife. The whole cornea is excised with scissors and used later on to cover the lens spatula. The iris is cut at 3, 6, 9, and 12 o'clock points and folded back over the sclera, exposing the zonule fibers, which are cut with scissors. The lens is covered with the excised cornea and scooped out on the lens spatula. The adhesions with the vitreous are cut, and the lens is put back into the globe until the recipient eye is ready to receive the graft.

Course.—Sutures were removed 10 days after transplantation under pentobarbital anesthesia and the eye was examined by slit lamp. In those experiments in which the lens was well in place behind the iris, the eye did not seem to show any more reaction than would be expected from an extracapsular lens extraction alone. A faint beam was observed in the anterior chamber, and the iris vessels were slightly engorged. The lens in these animals was crystal clear, although a streak-like opacity or a slight wrinkling of the capsule was occasionally observed.

The iris was frequently slightly drawn up, and in about half of the animals the anterior chamber was much more shallow in the upper half, where the incision was made. Closure at the angle, from an iris root adherent to the wound or from pupillary block, was probably the cause of the frequency of glaucoma in the first week after operation. If glaucoma occurred, the globe enlarged rapidly, the cornea became cloudy and vascularized, and, under these conditions, the lens was always cloudy when the globe was opened.

Complete luxation of the lens in the anterior chamber was rare, but forward tilting of the lens was frequent; subsequent subluxation and contact of the superior pole of the lens with the cornea was the

Fig. 8.—Excision of donor lens.

Fig. 9.—Spatula covered with donor cornea.

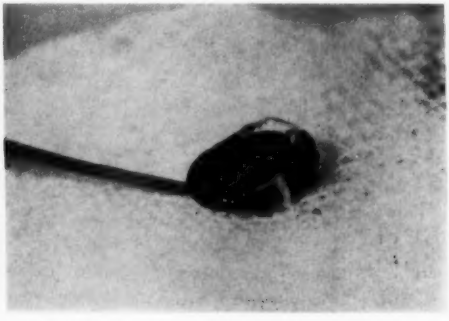


Fig. 10.—Donor lens ready for transplantation.

main factor in lens clouding in the first days after operation. It also accounted for a considerable number of cataracts in grafts which were clear for at least one month after transplantation. Slit-lamp examinations were only occasionally carried out during the first weeks after transplantation, so as to avoid subluxation of the lens when lifting the animal from its cage.

Apart from glaucoma and luxation, the lens may have become cloudy within the first one or two weeks after grafting because of trauma to the capsule or incision of the equator during preparation of the donor lens, although pressure on the lens was minimal and the donor lens was carefully inspected before transplantation.

Results.—Of a total of 92 lens homografts in rabbits, 32 turned cloudy within five days, either as a result of trauma during operation, or subluxation of the lens into the anterior chamber and contact with the posterior surface of the cornea, or as a result of rapidly developing glaucoma. Thirteen transplantations failed because the sutures gave way and the lens popped out. Four eyes were infected and developed a panophthalmitis. Six grafts were clear for a period of 10 days to 1 month but gradually turned cloudy within the next few weeks, either because of subluxation and contact of the cornea with the superior pole or as a result of glaucoma (Table 1).

Thirty-seven grafts, or a little over one-third of the total, remained clear for at least one month after transplantation. By

TABLE 1.—*Fate of Ninety-Two Homografts*

	Rabbits, No.
Panophthalmitis	4
Surgical failures	13
Lens cloudy within 5 days	32
Lens clear for 10 days	6
Lens clear for 1 month or longer	37

"clear" graft is meant no visible opacities for reflected light from the fundus as seen with the ophthalmoscope.

Slit-lamp examinations were only occasionally carried out in the first six weeks after grafting, because lifting the animals from the cage resulted in a number of lens luxations. Later on no such accidents happened, even though some animals were lifted by the skin of the neck, and the animals were examined with the slit lamp about every two weeks. Small granular opacities seen by slit lamp, which will be mentioned below, were neglected, and the graft was labeled as clear until they attained a sufficient size to be seen in reflected light (Table 2).

In this group of 37 clear homografts, 5 grafts remained crystal clear for eight months or longer, 3 of which were still clear when the animals were killed one and one-half years after transplantation. The graft of 8 months and the one of 12 months did not show any opacity in the slit lamp, although the latter was slightly subluxated downwards. The three grafts of 18 months all showed an irregularly shaped central

TABLE 2.—*Transparency Time of Thirty-Seven Lens Homografts Clear for One Month or Longer*

Time That Graft Was Clear, Mo.	Clear Grafts Developing Cataracts, No.	Animals That Died with Clear Grafts, No.
1	9	2
2	10	2
3	6	—
4	2	—
6	1	—
8	—	1
12	—	1
18	—	3 (killed)
	—	—
Total	28	9

"vacuole" in the embryonic nucleus of the lens, with a yellowish-colored wall which was visible only in the slit lamp. No opacities were present except in one of the three, where a few scattered granules were seen at the border of the fetal nucleus.

Four animals died with clear grafts within two months after transplantation, and 28 grafts turned cloudy. Of these 28 grafts, the cause of clouding was evident in 10 transplantations, as in 7 eyes the lens subluxated at the superior pole and touched the cornea, and in 3 eyes the lens was tilted forward, touching the cornea indirectly with the iris interposed. In three more grafts, malposition may supposedly have been a factor in the delayed clouding, as the grafts were drawn upward and tilted forward. In 15 grafts, no obvious mechanical factors were present to account for the development of cataracts.

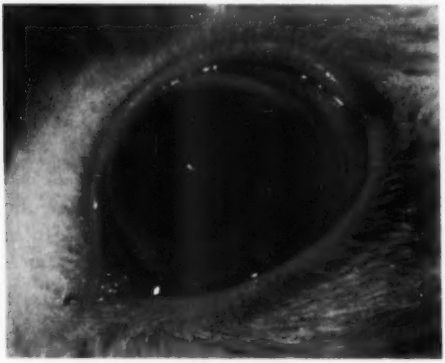


Fig. 11.—Crystal clear lens homograft 17 weeks after transplantation. The cornea is clear; the anterior chamber, of normal depth, and the pupil reacts to light. The lens was still clear when the animal was killed, 18 months after transplantation. (The photographer's image is seen in many of these pictures.)

In those eyes where the lens luxated into the anterior chamber, the clouding started at the superior pole, showing initially a grayish hue spreading gradually over the rest of the lens. Vacuole formation and clefts appeared soon after, and the lens became completely opaque. These grafts are of no further importance.

Interesting, however, is the development of cataracts in the 15 grafts for which no obvious mechanical reasons were present. The onset was shown by white granular specks throughout the lens cortex. These specks increased in size and number, and later on clefts, vacuoles, and streak-like opacities were superimposed until the lens was completely white. They were also noticed in the lens cortex of two grafts which became cloudy by subluxation after two months of clarity, suggesting that the cataractous process would have progressed in the following months if luxation had not intervened. The time of development of

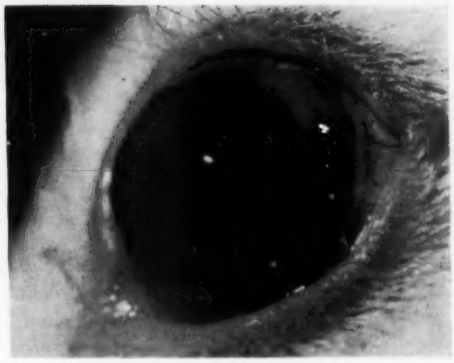
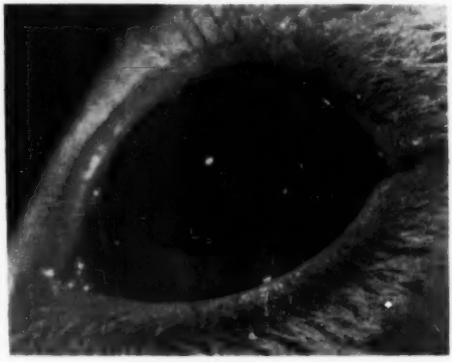


Fig. 12.—Lens homograft five weeks after transplantation. A vascularized and nearly healed corneal ulcer from a suture tract infection is seen at 10 o'clock position. The clear lens is well in place, and the pupil reacts to light. The lens suddenly turned cloudy in the second month after transplantation for no mechanical reasons.

Fig. 13.—Lens homograft five weeks after transplantation. Lens in excellent position and crystal clear. Cornea shows a slight degree of band-shaped keratopathy. Rabbit died seven weeks after grafting.



these cataracts varied between three weeks and three months.

In those grafts where the onset of cataracts was rapid, the iris vessels were engorged and sometimes extended over the anterior capsule. A faint beam was observed in the anterior chamber, and a few small cells were always present. Illustrative are three lens transplantations which were exceptionally well in place and crystal clear two months after operation. In two of them, the pupil was round and reacted to light. One transplant turned completely white within three weeks, three months after transplantation, with engorged iris vessels and a low-grade iritis. The second graft suddenly showed white dots in the third postoperative month accompanied by iris hyperemia and a low-grade iritis, and the cataract was mature in a month. In the third example, posterior synechiae were present at the superior lens quadrant. Nine weeks after transplantation, the iris became hyperemic, neovascularization started from the synechiae over the capsule, and white dots were scattered throughout the lens increasing in size and number; clefts and denser opacities followed, and within four weeks the lens was fully opaque.

These three transplants are mentioned in some detail because the grafts were in excellent position before and after clouding of the lens and because the low-grade iritis with a rather severe engorgement of the iris vessels seemed to be a response from the eye to the graft, strongly suggesting that, at least in these eyes, the lens homograft was antigenic to the host.

An attempt was made to sensitize the lens homografts which remained clear for 18 months by injection and implantation of rabbit lens one year after transplantation. Each of the rabbits received a subcutaneous and intramuscular injection of two homogenized rabbit lenses. Two weeks later, a similar dose was given subcutaneously and intravenously. After another two weeks, two lenses were implanted under the skin of each rabbit after incision of the capsule.

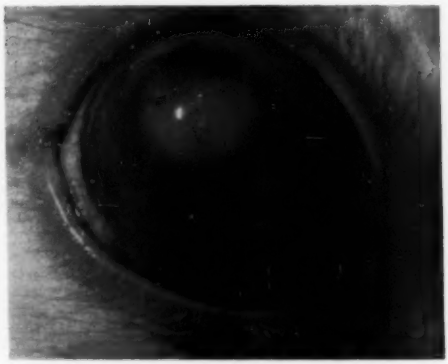


Fig. 14.—Lens homograft 29 weeks after transplantation. Lens was crystal clear and in excellent position for nine weeks. It suddenly turned cloudy, accompanied by low-grade iritis and neovascularization on the anterior lens capsule from the pupillary margin.

No reaction was seen in the eyes or in the grafts.

Effect of Graft on Host Cornea.—When the lens luxated or subluxated and made contact with the endothelium, the cornea became hazy and vascularization was the rule. However, corneal changes could also be observed in over one-half of the transplantations in which the graft was not in contact with the endothelium.

In four eyes a typical and pronounced band-shaped keratopathy developed between the first and fourth month after transplantation. In one eye the lens was slightly tilted but not in contact with the cornea. In the three other transplantations the lens was in excellent position. In one of them the lens remained clear for one and one-half years (except for the described central vacuole) and yet its keratopathy was extreme. After a superficial keratectomy, the cornea regained its normal transparency.

Less pronounced cases of band-shaped keratopathy were very frequent. In one-half of the eyes where the lens was in correct position, the cornea showed a fine mottled appearance in the region of the interpalpebral fissure. The mottling was limited to the subepithelial layers of the cornea and sometimes glistened like gold dust. It was occasionally revealed only on slit-lamp examination and barely visible with the

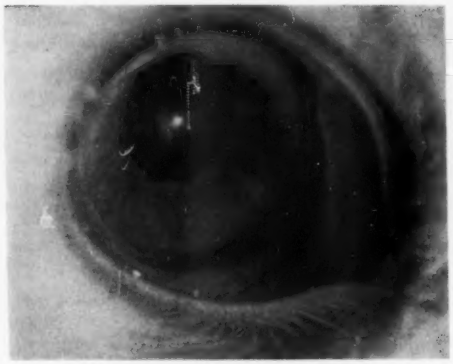


Fig. 15.—Lens homograft 30 weeks after transplantation. Lens in excellent position and crystal clear except for a yellowish central vacuole in the embryonic nucleus. Pupil reacts promptly to light. Although a pronounced band-shaped keratopathy developed two weeks after transplantation, the lens was still clear when the animal was killed, 18 months after grafting.

Fig. 16.—Lens homograft 34 weeks after transplantation. The lens is in excellent position and crystal clear except for a peculiar yellowish vacuole in the embryonic nucleus. Cornea shows a central band which glitters like gold dust on slit-lamp illumination. Pupil reacts to light. The transparency of the lens remained the same until the animal was killed, 18 months after transplantation.

naked eye on oblique illumination. Vascularization was usually absent, but a few capillaries could sometimes be observed in the marginal portion of the cornea.

Lens Heterografts

Monkey Lenses.—Fourteen monkey lenses were transplanted to the eyes of rabbits in the same way as were lens homografts. Transplantation of monkey lenses is a relatively simpler surgical procedure, because the lenses are small and flat as compared with donor lenses of young rabbits and are therefore easier to insert. Preparation of the donor lens of the monkey is slightly more difficult, because it is hard to separate the lens from the ciliary processes completely.

Of these 14 transplantations, 2 were surgical failures and 1 eye developed a panophthalmitis. Three lenses were cloudy the next day, and eight were still clear five days after transplantation. In the first series of transplantations, the eyes showed much more reaction in the anterior segment than was caused by lens homografts. The iris vessels became heavily engorged 5 to 10 days after grafting, and a beam and a moderate number of cells were seen in the anterior chamber. The iris vessels frequently extended over the anterior capsule, and most lenses were diffusely grayish and showed numerous clefts within eight days. One of them turned cloudy 11 days after transplantation.

In subsequent transplantations, drops containing 25 mg. per cubic centimeter of cortisone were administered locally four times daily, and cortisone ointment was applied at night, starting the fifth day after grafting. The iris vessels returned to normal in one or two days, but when cortisone was stopped the engorgement returned in 24 hours. Under continued local cortisone, the eyes remained white and three lenses remained clear for three weeks, four weeks, and six months, respectively.

All three lenses were slightly subluxated, the first two downward and the third forward into the anterior chamber. In the latter, the equator of the lens was actually glued in two or three places to the pupillary margin, and the subluxation is plainly visible in the photograph. This lens, nevertheless, remained clear for six months; cortisone was gradually reduced two months after transplantation and stopped in the third. Within a week, the iris flared up and cortisone was continued for another two weeks. A second flare-up occurred, and

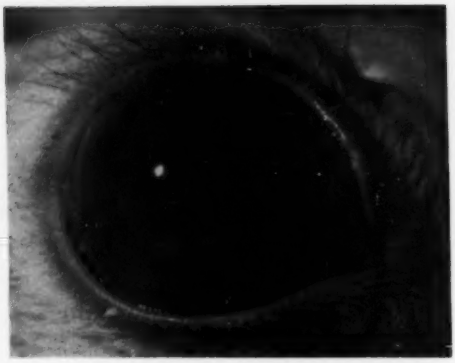


Fig. 17.—Rhesus (Macaca mulatta) monkey lens in rabbit eye seven weeks after transplantation. The inferior pole is slightly tilted into the anterior chamber.

subsequently a third, until the drug could be completely withdrawn in the fourth month after grafting. The lens capsule had always shown a few minor opacities, but the lens remained clear until, in the sixth month, vacuoles appeared under the anterior capsule accompanied by clefts in the cortex. Eight months after grafting, the lens finally was luxated into the anterior chamber, touched the cornea, and became completely opaque in two days. In the two monkey lenses which were subluxated downward, local cortisone did not prevent them from turning cloudy after three and four weeks, respectively; yet the drug considerably delayed the appearance of cataractous changes and the iris vessels remained normal. Both developed a grayish hue of the capsule, and clefts were seen soon after.

Band-shaped keratopathies did not occur, but in almost all eyes a pronounced mottling of the cornea in the central area was observed, with or without invasion of a few fine capillaries from the limbus.

Guinea Pig and Rat Lenses.—Two whole guinea pig and two whole rat lenses were implanted in the anterior chamber of four rabbit eyes. This was followed by extreme edema and vascularization of the cornea and by a severe iritis. The lenses gradually turned cloudy.

Embryonic Chicken Lenses.—Four lenses from chick embryos, which were incubated for 20 days, were implanted in the anterior chamber of four rabbit eyes. One week later, heavy edema and vascularization of the cornea occurred, and the lenses became completely opaque.

As the guinea pig, rat, and chicken lenses were in contact with the endothelium of the host cornea, corneal edema was to be expected. The reaction in these eyes was, however, much more intense than that which developed after subluxation of a homograft.

Histology

In almost all experiments in which the lens homograft turned cloudy, the iris and ciliary body were infiltrated with plasma cells and small lymphocytes. The same cells were also found in the anterior chamber and in the vitreous and were frequently lining the entire lens capsule. In those eyes in which the lens was still clear when the rabbit died, cellular reaction was entirely absent.

The reaction of the rabbit eye to the monkey lens was of the same nature and differed only in degree, as masses of plasma cells and lymphocytes were seen in the uvea, retina, and vitreous and great numbers of them were surrounding the lens capsule. Even in the eye with the monkey lens which remained clear for six months and rapidly turned cloudy after luxation into the anterior chamber, a moderate number of plasma cells were lining the lens capsule.

The lens epithelium in clear lens homografts was entirely normal, with a well-defined nuclear bow at the equator. In luxated lenses which touched the cornea, proliferation of epithelium, disappearance of the lens bow, and extension of the epithelium underneath the posterior capsule was the rule. In many lenses which turned cloudy after a clear period, the same changes were observed. In others, the epithelium was regular except for local proliferation, frequently under the anterior capsule. Many lenses of this group showed irregularities in the lens bow, in which only part of the nuclei dropped off to form fibers and part

migrated under the posterior capsule. In some of these lenses, not only were lens bows present at the equator but islands of nuclei were also seen further backward near the posterior pole with more intense staining of the fibers. These rudimentary lens bows seemed like abortive attempts to form new growth zones. In eyes where the cornea developed a macroscopically visible band-shaped keratopathy, fibrous tissue replaced the superficial corneal lamellae, but no anatomical substrate was found for the described gold-dust glittering of the cornea, which could be seen only in the slit lamp.

Subcutaneous Lens Grafts

Two lens homografts and two autografts were transplanted under the skin of the neck in rabbits. After 10 days, both the homografts and the autografts were surrounded by vascularized connective tissue and the lenses were completely opaque.

Histologically, the lens was encapsulated in fibrous tissue, the lens epithelium had considerably thickened, and the lens bow had formed peculiar islands of nuclei. The absence of inflammatory cells was striking.

Abdominal Lens Grafts

Two homografts and four autografts were inserted in the peritoneal cavity. After 10 days, one autograft was not encapsulated but was cloudy and lying loosely on the colon. All other grafts were surrounded by vascularized connective tissue and were cloudy, except for one autograft which was still partially transparent.

Histologically, the picture was identical to subcutaneous lens grafts except for one autograft where the fibrous tissue surrounding the lens was highly infiltrated with plasma cells.

Reversed Transplants

Normally the epithelial cells of the lens extend underneath the anterior capsule up to the equator; here the cells elongate to form fibers and are pushed into the cortex. It is not known what causes the cells to drop off at the equator instead of extending backward under the posterior capsule, and it would therefore be interesting to see what happens when the lens is transplanted with the original anterior surface backward, i. e., facing the vitreous. Four homografts were performed in this way, and the eyes were enucleated 14 days after grafting. Two grafts, unfortunately, had luxated in the anterior chamber; one eye developed glaucoma, and only the fourth graft remained crystal clear.

Histologically, the lens epithelium in all grafts completely extended under the posterior capsule now facing anteriorly and appeared as a thin monocellular layer of elongated epithelial cells. Slight irregularities in the nuclei of the lens bow near the capsule were perhaps an indication that a rearrangement of the nuclei was about to take place. Although the problem was only touched upon and not further pursued, the epithelial extension seemed to merit a short description.

Lens Material in Anterior Chamber and Its Effect on the Cornea

The striking frequency of pronounced mottling of the cornea and band-shaped keratopathy after homo- or heterotransplantation of the lens was further investigated. In preliminary experiments, whole guinea pig and rat lenses were implanted in the anterior chamber, but this was followed by extreme edema and vascularization of the cornea. If, however, the amount of lens was considerably reduced, mottling of the cornea developed in a great number of cases, as shown in Table 3. In 12 eyes, small pieces

TABLE 3.—*Number of Rabbit Eyes in Which Lens Substance in the Anterior Chamber Produced Mottling of the Cornea*

Donor Lens	Auto.	Homo.	Guinea Pig	Rat
Lens implanted	—	3	4	5
Mottling	—	0	3	3
Ground lens injected	2	5	8	—
Mottling	0	2	4*	—

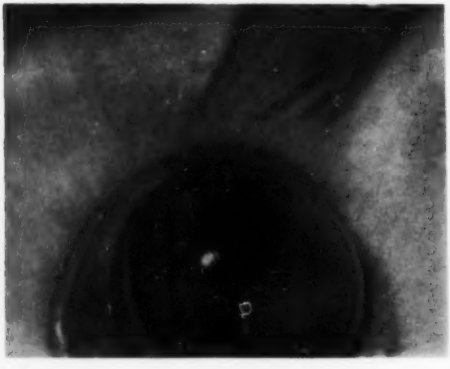
* In two eyes mottling occurred only after a second injection

of lens measuring between about 1 and 2 cu. mm. were implanted in the anterior chamber through a small corneal incision. In 15 eyes, lens ground in saline was injected in the anterior chamber after withdrawal of aqueous.

The mottling was not a transient, but a permanent, phenomenon and was strictly localized in the superficial corneal lamellae. The time of onset varied from six days to one month, and the intensity, from light to extreme, possibly dependent on the amount of implanted lens and perhaps on the extent of endothelial damage caused by implantation or even by injection under pressure. The mottling was frequently band-shaped, but it was sometimes ring-shaped or limited to only one sector of the cornea. In a few cases edema of endothelium and stroma preceded the mottling. Vascularization of the cornea was usually absent. Definite mottling of the anterior capsule of the host lens was observed in six cases, but it was not always associated with mottling of the cornea.

There can be little doubt that foreign lens material introduced into the anterior chamber has an effect on the cornea and perhaps on the capsule of the host lens as well. Therefore, mottling or band-shaped keratopathy, which so frequently occurred after transplantation of the whole lens, is presumably due to the lens graft itself,

Fig. 18.—Strong mottling of the superficial stromal layers after transplantation of a 2 cu. mm. piece of homologous lens material into the anterior chamber of the rabbit.



although it seems puzzling that a homograft which remains clear for 18 months could cause a pronounced band-shaped keratopathy. The large corneal incision or the corneal sutures were probably of very little importance, since no mottling was observed in cases where transplantation failed and the anterior chamber was closed without the lens having been inserted.

Histologically, fragmentation of superficial stromal nuclei was the predominant feature, with a few scattered unidentified cells, but actually no change was observed in the corneal lamellae in the hematoxylin-and-eosin-stained specimen.

Comment

The quiet course of the eyes after transplantation of homologous lenses as compared with the heavy engorgement of the iris vessels after the grafting of monkey lenses to the rabbit eyes suggests the presence of species-specific antigens. The species difference is also seen when guinea pig and rat lenses are implanted into the anterior chamber of the rabbit eyes. Although these grafts are necessarily in contact with the host cornea, they cause much more reaction than luxated lens homografts equally in contact with the host cornea. Apparently, the clouding of the monkey lens is the result of an antibody response from the host, because when it is suppressed by cortisone the iris vessels return to normal and the graft may remain clear for as long as six months after transplantation.

It would seem that the lens homograft also may act as an antigen and elicit an immune response from the host. Three lens homografts have been discussed which were crystal clear for two months and then turned cloudy in a relatively short time accompanied by iritis. As these lenses were in excellent position and were among the most frequently examined clear transplants, the sudden appearance of cataracts and iritis suggests an allergic etiology. A lower antigenicity of the graft may account for the more gradual cataractous changes which occurred in 18 other homografts or for the permanent

transparency of five homografts. It is also possible that donor and recipient were related and, despite the assurance of the dealer, transplantation was performed in inbred animals.

One may well argue that transplantation of the lens is a traumatizing procedure comparable to a contusion, eventually leading to cataract, or that the permeability of the lens capsule changed as a result of surgery, sensitizing the host to the lens proteins of the graft.

In preliminary experiments, the anterior chamber of a normal rabbit eye was opened and the lens was pressed with the lens spatula. Although more pressure was exerted than in the transplantation procedure, cataractous patches were observed in only one eye out of three and these patches were nonprogressive. In two other eyes, a piece of gelatin film, absorbable, (Gelfilm) was introduced into the anterior chamber and it remained attached on one side to the lens and on the other to the corneal endothelium. The lens was pulled forward when the anterior chamber refilled and remained in this position for three and seven days, respectively. Streak-like opacities which were observed in these lenses disappeared almost completely after the absorbable gelatin film detached itself spontaneously from the cornea. This demonstrates that both moderate pressure and pull on the lens may lead to cataractous changes, which are sometimes reversible but, in any event, are nonprogressive.

It is well known that contusion of the eye may lead to progressive cataractous changes. The onset is rapid, however, and a clear interval of two months is never seen. The one exception is the rosette in the posterior cortex, which may appear late but always remains localized. Massage of the lens capsule was used in the past to promote maturity of senile cataracts. Again, its effect could be observed almost immediately, i. e., in the first few weeks following massage. Finally, even a fairly large discission of the rabbit's lens capsule heals and the rest of the lens remains clear.

It is, therefore, difficult to believe that the three homografts suddenly turned cloudy after a clear period of two months as a late result of the trauma of transplantation or because of traumatic capsule changes permitting sensitization of the host by the lens proteins. Hence, the only other possibility which remains is that the proteins and polysaccharides of the *lens capsule* itself are antigenic and that a subsequent immune response of the host changed its permeability, leading directly to cataract formation or, indirectly, by now allowing lens proteins to pass and to sensitize the host. It could explain why so far all attempts in producing experimental cataracts immunologically have failed, because the lens capsule was not, or not sufficiently, sensitized, thus preventing lens antibodies from exerting any effect.

It is interesting that when the lens was transplanted to the peritoneal cavity or to subcutaneous tissue it stimulated the formation of dense fibrous tissue, seldom accompanied by cellular reaction. Yet when the graft became opaque in the eye it was always lined by plasma cells and hence a cellular response was expected, at least in the subcutis, particularly when the lens capsule was previously cut. When a lens graft in the eye turned cloudy, iris vessels frequently extended over the anterior capsule but never entered it. Similarly, subcutaneous or peritoneal grafts were not invaded by vessels, although almost any other homograft in subcutaneous tissue is readily vascularized. Lens material has apparently a unique property of preventing vessels from entering.

It is difficult to explain the frequency of band-shaped keratopathy and mottling of the cornea following transplantation of a homologous or heterologous lens. Yet it clearly depends on the presence of a lens or lens material. When transplantation failed and the cornea was closed without inserting the lens, mottling of the cornea did not occur. When homologous or heterologous lens material was implanted or injected into the anterior chamber, mottling of the cornea was noticed in a high percentage of experi-

ments. There was no correlation between the transparency of the graft and the intensity of mottling or band-shaped keratopathy. In fact, the most pronounced band-shaped keratopathy occurred in one of the eyes in which the lens remained clear for 18 months. As the presence of a foreign lens or lens material seems to be one of the prerequisites for its origin, the extent of endothelial damage due to surgery or implantation or to injection under pressure may account for its variable intensity.

When the experiments had been under way for over a year, a lens transplantation was reported in a blind human eye.[2] The transplant was still clear six months after operation. It seems doubtful, however, whether the viable lens can be used as a substitute for the Ridley procedure. The possibility of a homograft reaction in the graft or the cornea, apart from other surgical complications, would appear to discourage any enthusiasm in this direction.

Summary

Lens homografts transplanted to rabbits' eyes may remain clear for at least 18 months after transplantation or they may suddenly turn cloudy with accompanying iritis, after a clear period of two months. Other homografts remain clear for a considerable period but gradually turn cloudy.

Lens heterografts to rabbits' eyes turn cloudy in about 10 days, accompanied by a severe reaction in the anterior segment. The reaction to the monkey lens can be suppressed by cortisone, and this treatment prolonged transparency of one lens to six months after transplantation.

The clouding of lens heterografts and the delayed clouding of lens homografts is difficult to explain by the trauma of transplantation. The more likely alternative is that the lens capsule contains individual- and species-specific antigens and that its permeability changes after an immune response from the host.

The frequency of band-shaped keratopathy and mottling of the cornea following transplantation of the lens is related to the presence of foreign lens material, and pronounced mottling of the cornea can be produced by implantation or injection of homologous or heterologous lens substance into the anterior chamber.

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Hyaline Bodies of Ganglion-Cell Origin in the Human Retina

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In earlier studies my co-workers and I were able to demonstrate that hyaline bodies (corpora amylacea) of the human retina and optic nerve are a rather nonspecific finding. They may develop in senescense and under pathologic conditions from continuous or interrupted degenerating neurites (nerve fibers).[1-5] Very similar bodies are found as a result of degeneration of retinal astroglia,[6] perivascular glia,[7] or ganglion cells [8] under severe pathologic conditions. They may also occur as the final stage of hyalinization of microaneurysms in diabetic retinopathy.[2,9] The hyaline bodies of these different origins look histologically very much alike. They all are eosinophilic and may show a distinct lamellation. This latter fact gives them sometimes a cell-like appearance.

It is the purpose of this paper to describe a case which exhibits all stages of a hitherto unknown type of hyaline body formation by slow degeneration of certain ganglion cells of an otherwise well-preserved retina. The description of this new type of hyaline body is given with the presentation of all noteworthy clinical and histological findings of this case. Some of these findings may later prove to be of importance, since the significance of this type of hyaline degeneration of ganglion cells is not as yet understood.

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Report of a Case

The patient, a 73-year-old white man, was first seen in this clinic on Dec. 27, 1957. He had had cataract surgery O. U. about 10 years before and had no trouble and good vision in his right eye. He complained, however, of pain and progressive loss of vision in his left eye for several months before the first examination.

The patient's vision when first seen was 20/25+4 O. D. and finger counting at a distance of 2 ft. O. S. Both eyes showed aphakia. The right eye exhibited a clear cornea, an anterior chamber of normal depth, an intact vitreous face, and an essentially normal fundus. The left eye showed marked epiphora and photophobia. The left cornea exhibited extensive corneal bullae, staining, and marked edema of the stroma. The posterior surface of the cornea was covered with guttata. The anterior chamber was deep. The iris, vitreous, and fundus could not be seen because of the dense corneal edema. A diagnosis of aphakia O. U. and of advanced endothelial and epithelial dystrophy (Fuchs) O. S. was made. The patient was told that the left eye was beyond repair and should be removed, as it would become too troublesome.

The patient returned on March 12, 1958, to have the left eye removed. An enucleation was done on March 13. The eye was obtained for histological examination and immediately fixed in formaldehyde-ammonium bromide solution (Cajal's solution).

Method of Histologic Examination.—Half of the globe was imbedded in paraffin, cut in serial sections, and stained by routine methods of eye pathology. Frozen sections were made of the cornea, retina, and choroid

of the other half. These sections were stained with the silver carbonate methods of del Río Hortega as described by Scharenberg.[10] All illustrations presented in this paper are unretouched photomicrographs.

Results of Routine Histology.—The macroscopic examination of the left globe revealed it to be of normal size and shape. The anterior chamber was deep, and the iris showed a complete coloboma superiorly. The upper half of the pupil contained a dense white membrane which obviously was part of a doughnut-like formation of remnants of lens capsule and lens material. Most of the vitreous was liquified.

The microscopic examination of the paraffin sections, stained with hematoxylin and eosin, revealed the following changes. The corneal epithelium was irregular in thickness and exhibited vesicle and bulla formation. There was subepithelial scarring and loss of Bowman's membrane in some areas. The formation of hyaline warts could be recognized on some areas of the posterior surface of Descemet's membrane. The endothelial layer showed a remarkable decrease of its cellular nuclei which was most advanced in the corneal center. The anterior chamber appeared deep, and the filtration angle was open. Only remnants of the lens were found, which represented a typical Soemmering ring. The choroid showed some sclerosis of its larger blood vessels. The choriocapillaris, however, appeared to be very well preserved. The pigment epithelium showed some signs of degeneration. The retina exhibited some reduction of its ganglion cells in the macular region but was otherwise normal. Eosinophilic hyaline bodies were seen scattered all over the nerve-fiber and ganglion-cell layers of the retina (Fig. 1).

Results of Special Examination of Cornea, Retina, and Choroid with the Silver Car-

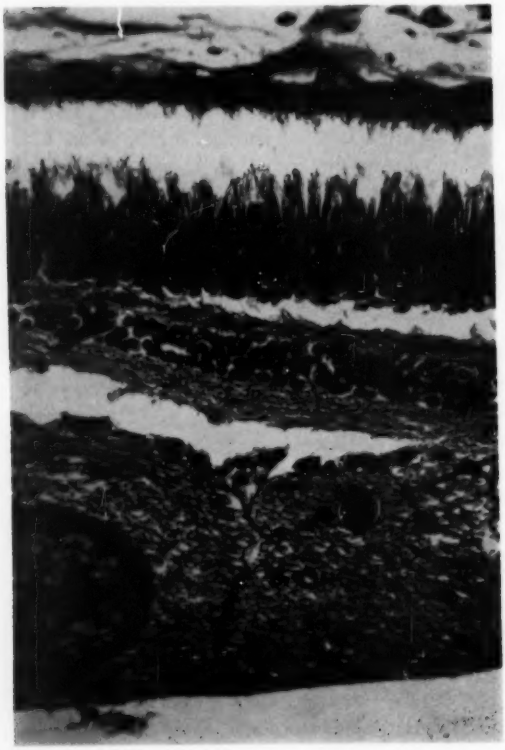

Fig. 1.—Routine section of the posterior retina with a large hyaline corpuscle at the limit between nerve-fiber layer and ganglion-cell layer (arrow). Hematoxylin and eosin stain, photomicrograph.

bonate Methods.—Silver-stained sections of the posterior layers of the cornea revealed interesting additional findings. An immense number of round wart-like excrescences were found to cover all of the posterior surface of Descemet's membrane. These bodies measured between 5μ and 50μ and were of the same substance as Descemet's membrane. They were always found to be in contact with Descemet's membrane, and no limit could be recognized between these bodies and the homogeneous substance of Descemet's membrane. The excrescences were most densely accumulated in the center of the cornea. The endothelium exhibited atrophy and loss of cellular nuclei which was most advanced in the central part of the cornea. There were also great numbers of round defects of different sizes in the endothelium that were obviously formed by the wart-like bodies on the posterior surfaces of Descemet's membrane. Many of these round defects represented through-and-through holes of the endothelium.

Silver staining of flat sections of the retina showed the arrangement of the retinal glia and neurons and many details of the structure of the single cells and fibers. The glia were essentially normal. There were no pathologic changes seen in the neurons of the outer retinal layers. Distinct pathology, however, was found in the nerve-fiber and ganglion-cell layers of the retina.

Figure 3 shows an area of a flat section of the innermost part of the ganglion-cell layer of the retina. All the relatively small ganglion cells of this area appear normal. However, the same ganglion cells of many other areas of this layer showed all stages of an interesting degenerative process. In the early stages of this process the ganglion cell exhibited coarse granulation of the protoplasm and the limits of the nuclei and processes became undistinct. The outstanding change of the later stages of this degeneration was an increasing hyalinization of the cell bodies. In the final stage only round hyaline bodies were left in the retina, while all the structures of the normal neurons were either destroyed or completely hyalinized. Some of these stages of degeneration and hyalinization are seen in Figures 2 to 7. Figure 1 represents an exceptionally large hyaline body of this kind as seen in this retina after hematoxylin and eosin staining.

It is interesting to note that this hyaline degeneration was often observed in ganglion cells which were surrounded by well-preserved blood capillaries or which were found directly beside larger blood vessels of the retina (Fig. 4).

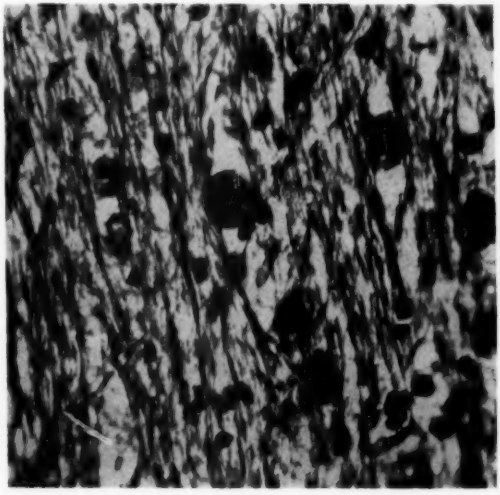

Fig. 2.—Low-power view of a hyaline corpuscle of ganglion-cell origin in the outer nerve-fiber layer. Ganglion cells in different stages of hyaline degeneration are seen around the corpuscle. Hortega method, photomicrograph.

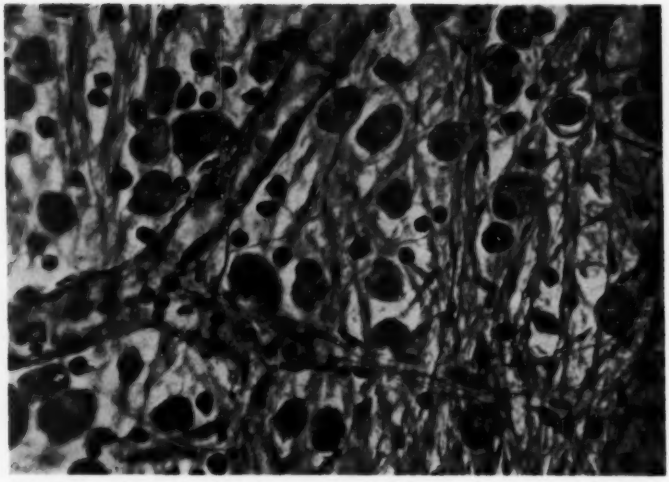

Fig. 3.—Flat section through inner part of the ganglion-cell layer of the retina which shows a blood vessel (*a*), normal ganglion cells, and one hyaline corpuscle of ganglion-cell origin (arrow). Hortega method, photomicrograph.

Figure 2 shows a typical late stage of hyaline degeneration of a ganglion cell in the zone between ganglion-cell layer and nerve-fiber layer at low power. It represents a round hyaline body which is lamellated and exhibits a dark-stained center.

It must be emphasized that the above-described hyaline degeneration of ganglion cells in this case was limited to the small ganglion cells of the innermost zone of the ganglion-cell layer. The deeper zones of the ganglion-cell layer also exhibited degenerative changes, but the changes of these cells were of a distinctly different type. Many of the large horizontal cells, for example, showed all stages of disintegration of the cell bodies and the protoplasm appeared swollen (Figs. 8 and 9). There was no hyalinization seen in these degenerating ganglion cells of the deeper zone of the ganglion-cell layer.

Further degenerative changes were found at the inner surface of the retina and in the pigment epithelium of this eye. The retina exhibited extensive proliferation of the flat astroglia which is normally found at the

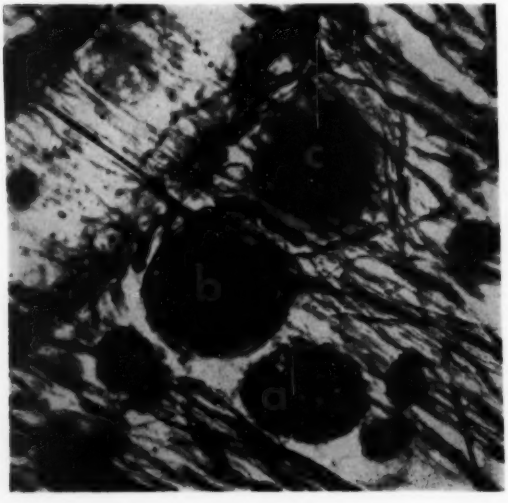

Fig. 4.—Flat section of the retina through the inner part of the ganglion-cell layer. Close to a blood vessel there are ganglion cells which exhibit different stages of hyaline degeneration. (*a*) A ganglion cell which shows accumulation of hyaline substance in the protoplasm; the cellular nucleus is preserved. (*b*) A more advanced stage of hyalinization of a ganglion cell; some of the cellular processes are still preserved. (*c*) a hyaline corpuscle is all that has remained of a degenerated ganglion cell. Hortega method, photomicrograph.

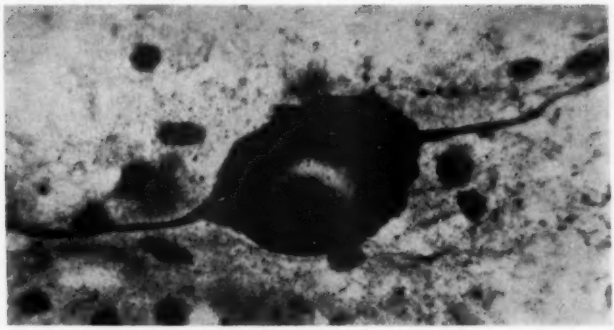

Fig. 5.—High-power view of a hyalinized ganglion cell, the nucleus and cellular processes of which are still visible. Hortega method, photomicrograph.

inner surface of the inner limiting membrane. These glial cells actually represented in some areas a complete new layer of flat cells with long processes. The pigment epithelium exhibited loss of pigment granula in many of the pigment cells. There were also large drusen (colloid bodies) which represented accumulations of hyaline substance between the pigment cells and Bruch's membrane.

Comment

The present case shows that the degeneration of certain ganglion cells of the inner zone of the ganglion-cell layer of the retina may result in the formation of round hyaline bodies. Such degeneration and hyaline preservation of retinal ganglion cells seems to be a new finding. The development of similar hyaline bodies from degenerating nerve fibers, astroglia, perivascular glia, and

Fig. 6.—High-power view of a ganglion cell in a later stage of hyaline degeneration than in Figure 8. The nucleus is no longer visible, but one process is preserved. Hortega method, photomicrograph.

Fig. 7.—Late stage of hyaline degeneration of a ganglion cell. A hyaline corpuscle is all that remained of the cellular body. The neurite is still visible. Hortega method, photomicrograph.

Fig. 8.—Large horizontal cells of the ganglion-cell layer (outer zone). One of the cells shows advanced degeneration of the cell body without hyalinization. Hortega method, photomicrograph.

microaneurysms has recently been demonstrated. Hyaline bodies of ganglion-cell origin were seen in a case of advanced retinal pathology.[1-9]

I have no explanation for the fact that the innermost cells of the ganglion-cell layer of this case showed hyaline degeneration while other ganglion cells of the same layer showed a different type of degeneration without hyalinization. I believe, however, that all the degenerative changes in this eye can be explained by the age of the patient and an additional postoperative degenerative process. This had involved the corneal endothelium, the retina, and the pigment epithelium. The fact that the hyaline degeneration of the retinal ganglion cells was often seen in areas with many normal-appearing blood vessels seems to indicate that this pathologic process represents "primary degeneration" and cannot be considered secondary to a vascular degeneration.

There can be no doubt that hyaline bodies of the retina are a nonspecific histologic finding. Many degenerating tissue elements may undergo hyalinization and result in similar hyaline bodies. I suggest the general use of the term hyaline bodies of the retina

Fig. 9.—Flat section through the outer zone of the ganglion-cell layer with a large horizontal cell in a late stage of degeneration without hyalinization. The cellular processes are swollen but otherwise well preserved. The adventitia of a blood vessel is seen at the left side of the picture. Hortega method, photomicrograph.

for all these corpuscles. A further description can be added to this term if the origin of the bodies is understood in a given case, as, for example, hyaline bodies of nerve-fiber origin, hyaline bodies of ganglion-cell origin, or hyaline bodies of neuroglial origin. It seems to me that the term hyaline body is better than that of corpora amylacea, since the substance of these bodies is hyaline and not amyloid.

In addition to the retinal changes, the present case exhibited degenerative changes of the corneal endothelium, the inner limiting membrane of the retina, and the pigment epithelium. The corneal endothelium showed the typical histologic findings of Fuchs endothelial and epithelial dystrophy. There were many deep round defects and also some definite perforations of the endothelial layer. These defects were found to correspond to numerous hyaline warts on the posterior surface of Descemet's membrane. The hyaline warts are the histologic equivalent of the cornea guttata as seen with a slit lamp.[11-13] The thinning and the perforations of the corneal endothelium on top of these hyaline warts of Descemet's membrane are the reason for an abnormal hydration of the stroma (edema and scarring) and the bullous keratitis which was seen clinically in this case. In the histologic slides of the present case and all other cases of cornea guttata reported by my coworkers and me,[11,12] the hyaline warts were always found to be in contact with Descemet's membrane. We consider the hyaline warts to be the result of pathologic hyaline deposition of endothelial cells in the process of primary degeneration.

A new layer of flat cells with long interconnecting processes was found to cover the inner surface of the inner limiting membrane of the retina. The existence of such flat cells on the inner surface of the posterior part of the normal human retina and the fact of the proliferation of these cells in degenerative retinal involvement were first described by Friedenwald,[14] who called them "endothelium-like cells." It was recently demonstrated that these cells represent a special kind of flat astroglia.[15] The proliferation of these cells in the present case is an interesting observation, and it is considered to be part of the degenerative process found in this eye.

Large drusen (colloid bodies) of the pigment epithelium on the inner surface of Bruch's membrane represented another degenerative change in this eye. It has been shown that such drusen may form by "transformation" of cellular substance within the pigment epithelium cells or by "deposition" beneath the intact pigment epithelium on the inner surface of Bruch's membrane.[16,17] The present case exhibited the latter developmental type of drusen. Both types of drusen are considered the result of primary or secondary degeneration of the pigment epithelium.

The present case permitted the demonstration and discussion of a new type of hyaline ganglion-cell degeneration in an eye with some other signs of a slowly progressive degenerative process. It seems to me that the detailed demonstration and classification of all of the types of such changes which the retinal elements may undergo under different pathologic conditions is the first step toward a complete understanding of retinal pathology.

Summary

Hyaline bodies represented the final stage of a peculiar hyaline degeneration of retinal ganglion cells in an eye of an old man with advanced corneal dystrophy following cataract surgery.

Department of Ophthalmic Surgery, University of Michigan.

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Alpha-Chymotrypsin (Quimotrase) in Cataract Surgery

Enzymatic Zonulolysis

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Joaquin Barraquer [1] is credited with the discovery of the practical use of α-chymotrypsin, a proteolytic enzyme, in facilitating cataract extraction. He demonstrated, both experimentally and clinically, that the enzyme, marketed under the trade name of Quimotrase, possessed anti-inflammatory properties and had a selective biochemical hydrolytic action on the zonular fibers. He hence introduced the term "enzymatic zonulolysis." Further claims were made that it had become possible to extract a lens regardless of the patient's age and to avoid inherent complications of mechanical zonulotomy resulting from scleral pressure or traction. Extracapsular extraction, lens capsule tears, and vitreous loss occurred to much less extent. The incidence of postoperative morbidity resulting from iridocyclitis and detached retina was also markedly lowered.

Stimulated by these encouraging reports, I was able to obtain a quantity of α-chymotrypsin to use on a varied series of cases that required cataract extraction.

Chemical Characteristics and Action

α-Chymotrypsin is manufactured under the trade name of Quimotrase by the P. E. V. Y. A. Laboratories of Barcelona, Spain. It is a proteolytic enzyme very similar to trypsin. It is obtained from veal pancreas as chymotrypsinogen, purified and crystallized to a white hydroscopic powder. The activation of chymotrypsinogen to chymotrypsin is brought about by the enzymatic cleavage of a single peptide bond. A vial containing 2 mg. of chymotrypsin is dissolved with 10 cc. of sterile isotonic salt solution to obtain a concentration of 1:5,000. Experimentally, Barraquer ascertained that at this dilution maximum biochemical zonulolysis resulted with no apparent subsequent deleterious effects to other intraocular structures. Four varieties of chymotrypsin are recognized: α, β, γ, and π. The α-type is more stable and possesses greater diffusibility through tissues.

Chymotrypsin, although grouped with trypsin as an endopeptidase, has certain differentiating features, mainly as follows:

1. Chymotrypsin curdles milk, hence shows a specific chymosinic property.

2. Trypsin causes intravascular clotting when given intravenously and can be considered toxic. Chymotrypsin shows no clotting action on the cellular constituents of the blood.

3. Both enzymes are further differentiated by the locus of their attack on the peptide bond. Trypsin alters the arginine-lysine, and chymotrypsin, the tyrosine-phenylalanine linkages. A similar biochemical effect is believed to take place in living cells.

4. The lysis of fibrin by chymotrypsin is 25% that of trypsin. Equal mixtures of trypsin and chymotrypsin exhibit lysis to the extent of 270% that of trypsin alone (Reiser, Roettig, and Curtis [2]).

5. The Barraquer group [3] demonstrated that α-chymotrypsin had a specific lytic action on the zonular fibers, both in the experimental animal and in humans.

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In 1932, trypsin was first isolated as a crystalline enzyme from beef pancreas. Chymotrypsin was similarly crystallized as a by-product of trypsin in 1935. Their selective properties of digesting nonviable cells and tissues was recognized clinically in general surgical conditions. In 1951, trypsin was subsequently introduced as a topical debriding agent. Prueter et al.,[4] in 1953, treated 60 patients that had necrotic and suppurative lesions with topical application of chymotrypsin. Skin burns, osteomyelitis, and infected wounds were treated by applying wet dressings containing 250,000 units of chymotrypsin. They were impressed with the marked rapidity with which necrotic tissue was digested within a period of two to five days.

Jenkins[5] treated a fairly large number of patients with a variety of ocular conditions, mainly, hematoma of lids, hyphemia, and iridocyclitis, with the intramuscular use of chymotrypsin suspension in oil. He was also impressed with the satisfactory results obtained.

In the United States three proteolytic enzymes are in use in general medicine. They are marketed as (1) Parenzyme (National Drug Company), (2) Chymar (The Armour Laboratories), and (3) Enzeon (George A. Breon & Company).

They are supplied in either an oil suspension (sesame oil) or an aqueous solution. They are intended for deep intramuscular use only. These products are manufactured from mammalian pancreas. Parenzyme is extracted from beef pancreas and contains trypsin, whereas the other two contain chymotrypsin. These drugs have been administered with satisfactory results in a large number of clinical conditions. Although the intramuscular use appears to be satisfactory, many promising results were obtained by their topical application. In ophthalmology they are particularly indicated in cases of traumatic lesions of the lids and globe that are complicated by an excessive amount of chemosis. Ophthalmologists, however, in general up to the present writing have been disappointed in the therapeutic results of these preparations in intraocular conditions, such as extensive hyphemia, vitreous hemorrhages or bands, and choroidal inflammatory lesions.

The current medical concept of the modus operandi of the proteases is believed to be an indirect one, working by some unexplainable mechanism affecting the other correlated enzyme systems of the body. Their main actions are supposedly anti-inflammatory and lytic. The quick response in clearing blood extravasations, edema, and necrotic tissue has been illustrated by a steadily increasing number of clinical studies. They have a wide margin of safety, and, even when administered intravenously to humans, they did not prove to be toxic. In persons, however, afflicted with hepatic or renal disease or with abnormalities of the blood-clotting mechanism, caution should be exercised when using these products parentally. Allergic reactions are very uncommon, and no unusual toxic reactions have been reported.

The only reference to the intraocular use of α-chymotrypsin, as it pertains to surgery of the lens, found by me was that reported by the Barraquer Clinic, of Barcelona.

Material

Over a period from June to September, 1958, thirty-two patients requiring cataract extraction were subjected to operation in which α-chymotrypsin was used intraocularly in a concentration of 1:5,000. The ages varied from 5 to 81 years. A variety of cataracts were selected which consisted of congenital, senile, and complicated types. I personally operated upon 12 cases, and the other extractions were performed by various members of the attending staff of the Brooklyn Eye and Ear Hospital. The surgical technique employed by me consisted primarily of removing the lens in capsule by the Verhoeff sliding method after performing one or two iridotomies.

Fig. 1.—Intracapsular cataract extraction with use of chymotrypsin, one month postoperatively.

Fig. 2.—Intracapsular cataract extraction with use of chymotrypsin, one month postoperatively.

Other members of the staff varied the technique, using either the Bell type of erysiphake, the lens forceps, or simply a muscle hook to aid lens extraction. The tumbling and sliding methods were both employed on different occasions, and extraction was performed through the round pupil or after a complete iridectomy.

Present Technique

α-Chymotrypsin (Quimotrase) is supplied as 2 mg. of dry white crystalline hydroscopic powder in a sterile vial. Ten cubic centimeters of isotonic physiological salt solution is used as a diluent to obtain a concentration of 1:5,000. Precaution was taken to use a sterile dry syringe to avoid contamination with other medications which could lessen its efficacy. Five cubic centimeters of the solution was aspirated in a syringe which was adapted with a blunt No. 24 gauge needle. The corneal section was made with either a Graefe knife or a keratome and was enlarged with scissors. The anterior chamber was gently and slowly perfused with 2 cc. of the α-chymotrypsin solution. The iris was thus bathed for approximately two minutes. A well-dilated pupil aided in allowing a greater amount of the enzyme to reach the zonular portion of the lens. An attempt was made to direct the stream behind the iris in order to reach the posterior chamber. One or more peripheral iridotomies or complete iridectomy were performed, and an additional 3 cc. of α-chymotrypsin was used, drop by drop, over the area of iridectomy and the zonula ciliaris above. In cases where iridotomies were performed, a blunt iris forceps was applied to tent the iris below the iridotomy opening and further irrigation was conducted slowly through the iris opening. Blood in the anterior chamber was irrigated when present, so as not to decrease the effectiveness of the enzyme. In the

Fig. 3.—Intracapsular cataract extraction with use of chymotrypsin, two months postoperatively.

Fig. 4.—Intracapsular cataract extraction with use of chymotrypsin, two months postoperatively.

majority of cases, mechanical breakage of the zonule with a muscle hook on the scleral surface was not required. In the early cases careful irrigation of the anterior chamber was performed to wash away any excess of α-chymotrypsin, in later cases this procedure was usually omitted. The corneal wound was properly coapted with 5 black 000000 nonabsorbable surgical (silk) sutures. Air was introduced in the anterior chamber with a No. 30 gauge short blunt needle. Any solution standing longer than four hours was discarded.

Results

In 8 operated-on eyes, moderate scleral pressure with a muscle hook was applied to aid in rupturing the zonular fibers prior to irrigation with α-chymotrypsin. Slight scleral pressure was used in nine eyes, and no external pressure of any kind was employed in the remainder of the eyes operated on. In the majority of cases, intracapsular extraction was completed with astonishing ease with use of the various surgical methods already described. In approximately half of the cases, after the second irrigation with α-chymotrypsin the lenses were seen to become either spherical or globular and to move forward into the anterior chamber, apparently as the result of the lytic action on the zonular fibers. Five cubic centimeters was usually sufficient in the majority of cases to produce this effect. The majority of the lenses presented an unusual amount of motility just prior to their extraction. This effect was noted after a waiting period of approximately eight minutes after the second irrigation with the proteolytic enzyme. In one case in which the iris prolapsed after the corneal section was made, there was impending loss of vitreous. At the completion of the operation the capsule was accidentally ruptured, and the vitreous eventually spilled. In my opinion, this was the result of faulty surgical technique. In another case, which presented a complicated cataract with extensive posterior synechiae following traumatic hyphemia, the lens was removed extracapsularly. No attempt was made to break the posterior synechiae, and irrigation with α-chymotrypsin failed to demonstrate any lytic action upon them. In the cases where the pupil had contracted, it was difficult to visualize the full effect of α-chymotrypsin upon the lens or zonular fibers. Nevertheless, after proper iris retraction, no difficulty whatsoever was encountered in removing the lens in capsule in most cases.

In two patients with congenital cataracts—one, 5 years of age, with a central nuclear type and another, aged 18 years, with an anterior pyramidal type—a very slight effect, if any, of lytic action after the use of α-chymotrypsin was observed. In spite of profuse irrigation with the enzyme no apparent effect on the lens structure or zonular fibers appeared to take place. In the first case a needling procedure was performed, and in the other case extracapsular extraction became necessary. No vitreous loss or undue hemorrhage, however, resulted. In both eyes the congenital cataracts presented a very firm attachment to the anterior face of the vitreous body.

Clinical Observations

In a considerable number of eyes the effect obtained after irrigation of the anterior chamber with α-chymotrypsin was indeed dramatic. After a period of approximately 10-15 minutes from the start of the operation, many of the lenses, especially the intumescent ones, were actually seen to assume the spherical or globular shape and also to show a greater degree of motility. In several cases, they were observed to move forward, thereby diminishing the depth of the anterior chamber. This effect was considered to be the result of the biochemical zonulolysis. There were no notable changes of the iris structures or its vessels. Excessive bleeding was not encountered. This could be attributed perhaps to a coagulating action which α-chymotrypsin may have had on the blood constituents. Inspection of the vitreous after the removal of the cataract

did not demonstrate any visible evidence of liquefaction, extrusion through the pupillary area, or gross changes in its composition.

The immediate and late postoperative course was uneventful. The general appearance of all eyes operated on even showed somewhat less reaction than normal, which could be attributed to the anti-inflammatory factors of the α-chymotrypsin. Subsequent study of the eyes several weeks after surgery did not reveal any late sequelae, such as unusual iritic involvement, late vitreous changes, corneal edema, or retinal detachment. This applied regardless of whether the excess of α-chymotrypsin was lavaged from the anterior chamber at the completion of the operation. Healing of the corneoscleral wound proceeded at an apparently normal rate, and at no time was there evidence of allergic manifestations.

Comment

In order to obtain optimum results, the eyes prior to cataract extraction should be somewhat in a state of hypotony. In hypertonic eyes, especially in the presence of an intumescent cataract, it is advisable to reduce the intraocular pressure by administering 250-500 mg. of acetazolamide (Diamox) intravenously one hour before surgery. A well-dilated pupil allows the proteolytic enzyme to reach the posterior chamber or the zonular area more effectively and thereby accelerate the degree of zonulolysis. It is possible that in a certain number of cases complete biochemical resolution does not occur. This was illustrated clinically by observing some of the lenses which showed small tags of zonular remnants after extraction. Slight scleral pressure in some instances was required in order to produce a degree of mechanical rupture of the zonule.

Summary

Thirty-two patients presenting varied types of cataracts were operated on with the use of α-chymotrypsin (Quimotrase), which demonstrated the effects of enzymatic (chemical) zonulolysis.

Various techniques were employed in performing the surgery, namely, tumbling or sliding of the lenses with the use of either lens forceps or the Bell erysiphake. Slight, moderate, or no scleral pressure was used to aid in mechanically rupturing the zonular fibers prior to lens extraction.

Aqueous α-chymotrypsin in a concentration of 1:5,000 was used to irrigate the anterior and posterior chambers. To reach the zonula ciliaris approximately 5 cc. of the solution was needed and a waiting period of approximately 10 to 15 minutes was allowed. This resulted in satisfactory biochemical zonulolysis.

The majority of the lenses were actually seen to become globular and to demonstrate a greater degree of motility. Subsequent shallowing of the anterior chamber resulted. In this series of cataract operations in which α-chymotrypsin was used to produce biochemical zonulolysis, the effect in many instances was dramatic. All of the lenses were removed intracapsularly with facility with the exception of four eyes. In two eyes this was not possible because of faulty surgical technique. In two cases of congenital cataracts little or no effect of chemical zonulolysis was observed. Loss of vitreous resulted in only one eye in the complete series.

It should be emphasized that α-chymotrypsin must be used under sterile precautions and must not be contaminated with other solutions which may weaken its efficiency. A well-dilated pupil, absence of excessive hyphemia, and a hypotonic eye will result in producing a more satisfactory effect of enzymatic zonulolysis.

The immediate and late postoperative course was uneventful. The corneoscleral wound healed properly at a normal rate. No unusual late changes were noted in the iris or vitreous body when studied biomicroscopically. The proteolytic enzyme did not appear to have any lytic effect on synechiae.

With the future use of this special enzyme in a greater number of cases, its true value

in cataract surgery will eventually be determined and established.

160 Henry St. (1).

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An Improved Binocular Magnifier

WM. B. HUBBARD, M.D., Flint, Mich.

Binocular magnifiers worn with a head band are routinely made to be worn without glasses or with single-vision glasses. These magnifiers are easily adjusted upward. However, it is impossible to adjust them downward over glasses beyond a certain point. The user thus at times may have to tilt his head awkwardly down and his eyes up. He cannot get the magnifiers down far enough to use with bifocal glasses.

In order to overcome this difficulty a "Twin Loupe" * (in this instance, a bifocal pair, 3 × magnification above and 1¾ × below) was modified as follows (Figure).

With a metal saw the aluminum portion of the magnifier was divided horizontally into two halves. The anterior section was dropped straight down approximately 1⅛ in. The two halves were bolted together in the new position with one piece of flat connecting metal on each side.

The new magnifiers can easily be moved up or down as desired, although this is seldom necessary.

302 Paterson Building (3).

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* Plastal Corporation, 568 Palmer Rd., Yonkers, N. Y.

Superficial Keratitis Due to Plastic Foreign Bodies

T. D. DUANE, M.D., Bethlehem, Pa.

There has been a recent fad in women's dress which has produced a resurgent demand for stiff billowing skirts and petticoats. Relatively heavy and coarse-meshed plastic material, called bouffant, has been employed by garment manufacturers to attain the desired shapes. The plastic material has a tendency to flake when cut or bent. The flakes fly into the atmosphere and not infrequently alight upon the cornea, where they may induce a low-grade keratitis. Experience with over 75 of these cases is described below.

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Etiology

Bouffant (modified nylon) is a stiff plastic material which flakes into octagonal or hexagonal thin crystals about 0.5 to 1

mm. in diameter when it is sheared. The organic constituents seem to be inert as far as chemical irritation to the eye is concerned. No changes of a chemical type have been observed, such as have been described in instances of artificial silk keratitis.[1] All of the difficulties seem to arise from the physical presence of these minute foreign bodies on the superficial layers of the cornea.

Pathology

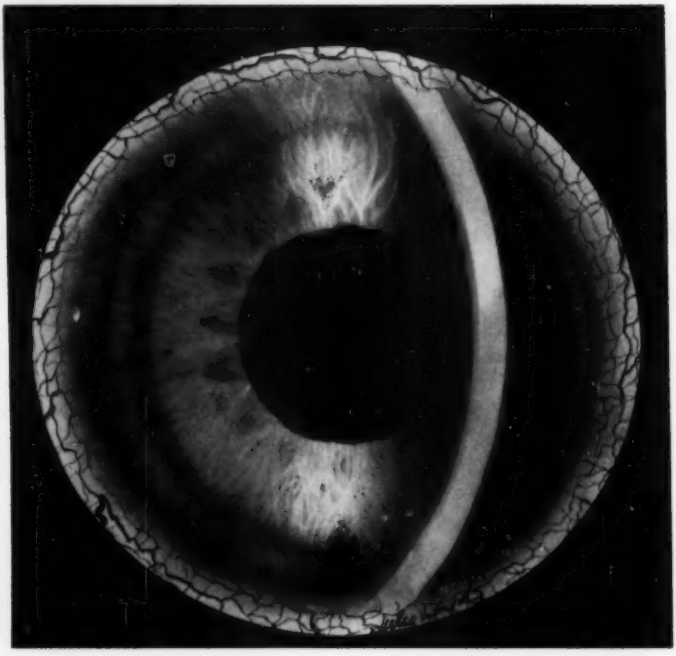
The cornea does not stain; however, fluorescien forms a green ring around the transparent nonstaining foreign bodies. Apparently they are lodged in the outermost flattened layers of the corneal epithelium and are covered by the film of tears. Fortunately, none of these eyes have been examined under the microscope.

Symptoms

The complaints of patients afflicted with this malady are typical of those induced by any nonspecific foreign body. There seems to be no relation between the number or size of the particles resting on the cornea and the subjective feelings involved. Frequently one will be requested to examine an eye which has "sharp sticking pain" produced by one or more plastic foreign bodies, while the fellow eye may be carrying five or six which have aroused no symptoms whatever. After slit-lamp examination, it is possible to startle patients who have come for a routine refraction by announcing to them that they work around bouffant. Some patients present evidence of moderate increased tearing, but mattering and photophobia are seldom encountered.

Diagnosis

The diagnosis can be readily established with the biomicroscope. Other than an occasional perilimbal injection, all of the findings are restricted to the cornea epithelium. It is almost impossible to discern the foreign bodies without the aid of magnification. One should be suspicious of their presence not only in locales where



these garments are manufactured but anywhere that women wear and adjust such garments, which certainly includes the entire United States. With garment workers, it is advisable to screen almost every patient for the possible presence of these particular foreign bodies. As stated, staining may be of assistance, but usually it is an unnecessary procedure. The organic material is well demarcated, especially with indirect retroillumination or with sclerotic scatter (Figure). The examiner must be careful not to ignore the upper one-third of the cornea, which is often hidden by the overriding upper lid. To the uninitiated, the plastic particles resemble air bubbles or common detritus when first noticed, and the tendency is to ignore the observation. If one moves the lid or asks the patient to blink, the plastic foreign bodies remain stationary and therefore warrant closer scrutiny. Seldom does one see these plastic flakes in the palpebral or bulbar conjunctiva, although they have been discovered beneath the upper lid.

Treatment

The particles must be removed mechanically with a spud, needle, or some other metallic tool. They will not dislodge with cotton swabs, and routinely they cannot be washed from the corneal surface. After instillation of a local anesthetic, they can be gently lifted from their epithelial bed under direct observation via the biomicroscope. If one employs a No. 25 caliber needle on a 2 cc. syringe and if one directs the light beam slightly to the side, one will have no difficulty in removing them. If much of a corneal abrasion results, antinot routinely necessary. No other medicabiotic drops may be indicated, but these are tion or treatment is required.

In at least one instance when four particles were experimentally applied to the cornea of a volunteer, they spontaneously disappeared within several days. It is assumed that they were eventually washed away by the tears and lid action or by some other protective mechanism of the eye. How often this occurs in affected patients is at present unknown.

Prevention

Prevention is by means of shielded spectacles or goggles, which are unpleasant during cool weather and intolerable during the hot months. If the stiff bouffant is sewed under or covered by some other fabric while it is being worked, the incidence of patients requiring attention is greatly reduced. To date there is no simple way to prevent this form of keratitis when bouffant is sheared, sewed, or folded. Even messenger boys and janitors who work in the area of its manufacture are not immune.

Prognosis

The prognosis is excellent. All cases have responded favorably to simple removal of the offending material. Recurrences up to five times with 25 individual flakes have been seen in our series with no serious sequelae or permanent defects. The eyes heal with no trace of a scar.

Summary

Bouffant, a form of nylon employed in the manufacture of stiff petticoats, has a tendency to flake when the material is worked. These flakes may lodge upon the corneal epithelium, where they either remain quiescent or produce a low-grade keratitis. They can be readily discerned with the biomicroscope and under this magnification they can be atraumatically removed with a fine-gauge needle, leaving no permanent defects.

Dr. Gaylord W. Ojers assisted in the observation and treatment of these patients. Dr. F. H. Adler arranged for the drawing by Miss Julia Lloyd.

619 Main St.

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An Improvement in the Use of the Wadsworth-Todd Cautery

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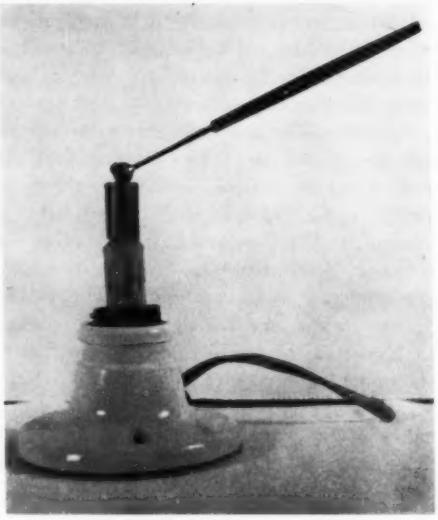
The use of heat topically to stop surface bleeding, employing metal cauterizing points of sufficient temperature, goes back to the ancients. Heated in a flame or in a brazier, the cautery-iron of mediaeval ophthalmologists was also used in a variety of other conditions. One of its more modern forms was that of Wadsworth, later modified by Todd,[1] often used to touch bleeding spots during surgical procedures. With scientific advancement, instruments activated by electrical methods have been introduced, but these generate heat too high for safety. The Hildreth Electric Coagulator[2] represents an improvement over other preceding methods, but there are certain drawbacks which make its use difficult at times.

A practical appliance would have to incorporate modifications to meet the following criteria: 1. The contrivance must be uncomplicated, making it a reliable instrument. 2. The metal or alloy selected must retain heat for a long time. 3. The applicator must be sufficiently hot not only for application to the eyeball but for lid and muscle surgery as well. 4. Safety in the operating room is essential so that anesthetic vapor is not ignited by sparks or an open flame. 5. Finally, the instrument must be so designed that it can be rapidly and easily applied to tiny as well as larger bleeding surfaces.

With these objects in mind, the well-known Wadsworth-Todd cautery was chosen and, instead of an open flame, a simple small electric heating unit was devised to heat the cautery so as to keep it constantly at a sufficient temperature for instant use. For this purpose a soldering point was selected which according to the manufacturer's specifications furnishes a tip temperature of 1000 F.*



The heating unit with the Wadsworth-Todd cautery in place.

The tip was then filed down to a flat surface and a fine hole was drilled through this surface just wide and deep enough to accommodate the platinum point of the Wadsworth-Todd cautery. There is a Bakelite handle made by the same manufacturer which can be cut down to size and into which the base-thread of the tip fits accurately, or any other receptacle accepting the same thread can be used. The ensembled parts are then fitted into any suitable heavy base, as shown in the Figure. A short piece of copper tubing of sufficient width and length has been slipped over the soldering tip to give it a finished appearance, but, if so desired, this can be omitted.

The described heating unit for maintaining the Wadsworth-Todd cautery at a con-

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* Obtainable from Ungar Electric Tools, Inc., 4101 Redwood Ave., Los Angeles 66.

stantly adequate temperature has been employed for some time and has proved to possess considerable advantages. Experience has shown that it can be used to coagulate bleeding spots instantly on the scleral surface or at a limbal incision by lightly touching each with the platinum point, which may be applied sideways to control general oozing from scratch incisions, while larger areas in the lid or muscle may be touched with the protuberance on the copper bulb. Excessive bleeding from a canthotomy can be stopped quickly in this manner. Although it is better to have the field sponged dry before applying the instrument, it is sufficiently hot so that diffusion of the heat is minimized even in more or less wet areas.

The advantages of a small hand instrument like this are self-evident. It may be used to cauterize the surface of a corneal ulcer much more delicately and safely than with the galvanocautery. Actual use has shown that it can be used on bleeding areas at least six times before requiring reheating, which again takes only a few seconds.

The cautery is sterilized together with the other surgical instruments in the preferred manner as desired. The electrically connected heating apparatus having been previously placed on a table adjoining the operating table where it is easily reached, the platinum point is inserted into the hole of the superheated modified soldering point. The cautery handle never becomes hot, is always sterile, and the instrument can be lifted and replaced at will during the course of the operation. It is evident that there is no open flame; no sparking can occur, and danger of explosion in the presence of general anesthetics is thus avoided.

2007 Wilshire Blvd. (57).

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Clinical Notes

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Canthotomy

If the external canthus is clamped with a hemostat before the incision is made, annoying bleeding will usually be prevented (Figure).

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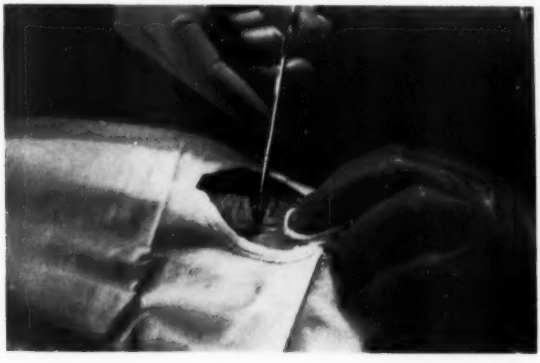
Removal of Blood from Anterior Chamber

When blood enters the anterior chamber after the section for a cataract extraction, the usual procedure is to wash out as much



blood as possible by irrigation and then to remove the clot with smooth capsule forceps.

If after irrigation the tip of the irrigator is held next to the clot and the pressure on the bulb is released, creating suction, the clot is sucked partly into the irrigator tip, blocking it, and sufficient suction is created to hold it while it is removed from the anterior chamber.

The irrigator preferred consists of a small silver irrigating cannula with Luer hub which is attached to an adapter in a ¼ oz. rubber Acepto bulb.

By this method it is not necessary to introduce another instrument into the anterior chamber and the danger of grasping the iris with the forceps is avoided.

129 Clinton St.

Annual Review

Lids, Lacrimal Apparatus, and Conjunctiva

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Introduction

The literature concerning the subjects of this review has again been too large to cover fully. I shall not attempt it. Many articles are not included because they reiterate points which were included in last year's review or some previous review. An obligatory perusal of the literature impresses one with the amount of repetition (or perhaps confirmation) which appears. Many articles are not included because of inadequate translations of some foreign contributions, although I have done my best to overcome this obstacle. Many articles are not included because I have overlooked them, and I apologize to the authors and to my readers. No deadline can be drawn as to the beginning and end of a yearly review, and hence some of the reference dates may seem remote. Many good articles from early 1957 or earlier have become available since last year's review was finished.

Lids

Ptosis and Allied Conditions.—Ptosis accounts for its usual share of attention. Several new operations and variations of old operations have appeared. They still attempt to elevate the eyelid by utilizing the levator, the frontalis, or the superior rectus, and again this year the substitute power operations, i. e., the frontalis and superior rectus procedures, have their champions. Swan and Keizer [1] offer the only new levator-shortening operation. It appears to be an excellent procedure. The tarsus is left intact. I have never worried about excision of part of it, but Swan and Keizer feel that it should not be resected. They undermine the conjunctiva almost to the fornix and then dissect the superior surface of the levator to the orbital septum. Five sutures are placed in the levator at this level. The orbital septum is then separated from the levator and allowed to retract, permitting advancement of the muscle without including the septum. This is important in preventing lid lag when looking down. This is a complication of levator resection which we see too often, and I believe that operations which include the septum in the sutures are much more apt to produce it. After resection of the excess levator the five sutures are fixed and buried in the tough tissue anterior to the tarsus near the lid margin. The lateral wings of the aponeurosis are not cut. Sometimes a separate row of sutures is used to create a lid fold. Swan and Keizer report excellent results. The operation is simple and is certainly more physiologic than most levator-shortening techniques. My limited experience with the operation indicates that it is effective. I was sorry that I did not use a row of lid-fold sutures on two eyes, as a condition simulating blepharochalasis resulted. If the lid can be satisfactorily raised without production of a lid lag, this operation is a good contribution. Jain [2] reports 16 appreciable lid lags in 26 satisfactory levator-shortening operations. Because of this, he feels that ptosis should be slightly undercorrected. I do this often but not intentionally.

The question of how much levator to resect is always a problem. Sokolić [3] solves it by modifying the last stages of the Blaskovics operation. He turns the lid to its nor-

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mal position and elevates it to the desired degree. The levator with its clamp or sutures is pulled downward, and the sutures between lid and levator are placed from the anterior surface of the lid. The globe is protected with a glass spatula in the fornix. This seems like a good idea, except that the degree of relaxation of the anesthetized muscle or the muscle in the anesthetized patient would be difficult to judge, and how does one decide how hard to pull?

Verzella [4] utilizes a broad strip of orbicularis muscle, mobilized and passed under the superior rectus, as a new variation of this type of operation.

Two authors modify the Friedenwald-Guyton sling operation. Weber [5] avoids the nasal notch in the lid margin by adding a separate suture from the center of the lid margin to the center of the brow. This suture is removed in one week. Ohashi [6] makes the lid margin lie with a more even arch by placing two triangular buried sutures, with the bases joining at the brow level and with the apices at the tarsal level, at points dividing the lid into thirds. The use of two triangles rather than a rhomboid seems to make this frontalis-sling procedure better than its predecessor.

Fonte [7] states that fascia lata strips between the lid and frontalis are easily placed and that this operation can be used in any variety of ptosis. He reports good results in 100% of cases; a good average.

Henderson's [8] operation deserves some comment. He makes three stab incisions in the lid to the anterior surface of the tarsus. Double-armed nonabsorbable sutures are fixed to the tarsus at the depths of these incisions. They are carried upward along the plane of the orbital septum to stab incisions over the brow. An important feature is that before they emerge from the upper incisions the needles are made to dip into the orbital septum at the point of its reflection from the periosteum of the frontal bone. I would think that this would negate the action of the frontalis in moving the lid—at least, to a degree. Henderson states that this operation is applicable to almost all types of ptosis. He states that the operation is more easily mastered by graduate students, who may settle where they will do only an occasional ptosis operation, than are the surgical techniques of levator resection, etc. Granting that Henderson's operation is a good one, would it not be better, if it is impossible to train the graduate student to do the proper ptosis operation well, to train him to refer his ptosis patient to someone who can? Poor choice of procedure in ptosis surgery is discussed by Carbajal.[9] In an analysis of 142 ptosis operations done by various surgeons at a Los Angeles hospital he emphasizes that some surgical techniques are good in certain cases but misapplied in others. He feels that we should refrain from making all patients suit a favorite technique but should choose a technique that suits the patient. His series brings out the fact that once a mistake is made in the choice of the first procedure or in the actual surgery, the chances of success in the second attempt will not be as good.

Bames [10] reports an operation for what he terms frown disfigurement and ptosis of the eyebrows. This is, in a sense, an ophthalmologic problem, as the facial disfigurement caused by photophobia, asthenopia, etc. may become chronic and is complained of by our patients. Bames treats it by a surgical cross hatching of the frontalis insertion, a resection of the corrugator supercilii, and an avulsion of the pyramidalis nasi. A smooth placid forehead results with little adverse side-effect. Numbness to the vertex may result, but it is not complained of by the happy patient.

Blepharospasm of a severe type is sometimes seen associated with Parkinsonism. Urist [11] reports several cases of this condition. He discusses the various treatments which have been used, such as alcohol injections, division of the facial nerves, and resection of the orbicularis. He treated three severe cases by placing Friedenwald-Guyton slings as used in ptosis. Good results were obtained. Urist rationalizes that the orbicu-

laris spasm in this condition is prolonged, while the brow spasm is of short duration. The sling allows the controllable frontalis to pull on the uncontrollable orbicularis and hence to break the spasm and allow the eyes to open.

Lewallen [12] reports a case of traumatic ptosis which was complicated by a perplexing retraction of the opposite uninjured eyelid. It was proven to be an innervational "secondary deviation" caused by attempted elevation of the injured eyelid. This article is made a little confusing by the unfortunate reversal of the pictures.

Tumors.—A good article on carcinoma of the eyelids and canthal region appeared in *Geriatrics* last year. It was mentioned in last year's review but was inadequately covered. Brown and Fryer [13] emphasized the necessity of biopsy before undertaking treatment. Treatment by surgery or irradiation must be adequate. Often reconstructive surgery is necessary after irradiation, and it is made more difficult by the tissues having been irradiated. Skin affected by chronic irradiation dermatitis should be replaced to prevent the development of carcinoma. They describe spontaneous reconstruction after excision. I have seen large defects after dermatological treatment of tumors by curettage and desiccation reconstruct themselves with surprisingly little deformity. If these defects involve the lid margin, however, they are less apt to behave favorably, and I feel that reconstruction is better than optimism. Brown and Fryer bring out the fact that eyelids reconstructed by flaps are essentially akinetic and hence less pleasing cosmetically and functionally. I did not know that the plastic surgeons were aware of this. The authors feel that every patient with an eyelid tumor capable of metastasizing is a candidate for neck dissection. Should this be decided upon, it should be complete, including the removal of the sternomastoid muscle and the jugular vein. They state that tumors in the region of the tear ducts should be treated surgically, as adequate irradiation causes damage to these structures. Surgery often causes more damage, and one should carefully weigh the possible results and choose the less of the two evils. Here there is no subsitute for the experience of having seen the good and bad results of both methods.

Caution with regard to neck dissection is brought out by Crile.[14] Statistically there is no proof that prophylactic resection of regional nodes is any more effective in cancer control than is therapeutic resection after regional metastases are present, he says. He feels that much of the morbidity of extensive surgery indiscriminately applied can be avoided by first using a limited operation when this has a good chance of controlling the disease without jeopardizing the success of a subsequent more extensive procedure.

An article on biopsy by Caro [15] advises a cold-steel surgical removal of a representative area, including a small area of normal tissue. He asks that a gross description of the lesion be submitted together with the specimen. I think that the pathologist must be impressed with the fact that he is being furnished with a specimen for diagnosis rather than an excised tumor. Otherwise, the words "inadequate" or "incomplete" find their way into his reports with too much frequency for medicolegal comfort.

Two articles on benign calcifying epithelioma of the eyelid appeared last year, one by Roberts [16] and one by Mitchell and Newell.[17] This condition is often mistaken for a sebaceous cyst. The upper eyelid is the only site of ocular involvement. Yellowish-gray firm tumors are embedded in the skin. Histologically they are composed of irregular clumps and bands of large basal cells with large basophilic nuclei and well-marked nucleoli. Areas of "ghost cells" are seen. They form eosinophilic masses which may calcify, although only about 25% of them do. They are most probably derived from epithelial elements which have the potentiality of differentiation into hair follicles, sebaceous glands, or apocrine glands. They are diagnostically significant in that they are benign.

Another benign lesion which has been previously discussed is keratoacanthoma. Cohen [18] states that the pathologist may report a prickle-cell epithelioma unless he is furnished with a history of the duration and growth of the lesion, as well as its gross description.

Agarwal and Shrivastav [19] report a case of amyloid tumor of the eyelids. There was extreme generalized thickening of the lids with nontender nodules, which proved histologically to be amyloid degeneration. They thought that it was secondary to an inflammatory process, probably trachoma.

In a good discussion of the pigmented skin lesions Becker [20] reports that malignant melanomas are diagnosed clinically in less than 50% of instances and that here again biopsy is of great importance. He feels and quotes others who feel that biopsy cannot be incriminated as a cause for metastasis. However, he does not object to removal of the entire lesion for biopsy. On the eyelid this can be difficult.

Statistical studies of eyelid tumors make interesting reading for interested parties, but they do not offer much that has not been said before. However, a study of 617 pathological specimens is large enough to be sited. Welch and Duke [21] found about 85% of the lesions received to be benign papillomata, nevi, chalazia, cysts, xanthelasmas, verrucae, inflammatory lesions, etc. Of the 88 malignant lesions, 68 were basal-cell carcinoma; 9 were basosquamous carcinoma; 8 were squamous-cell carcinoma; 2 were carcinoma in situ, and 1 was a Meibomian gland carcinoma. It is of interest that only 56% of the basal-cell carcinomas were correctly diagnosed clinically. This scores another point for the importance of biopsy.

Hemangioma is a lesion which we often see involving the eyelids of infants. We are very often perplexed as to what to do about them. We know that many of them will regress if we wait long enough, but we and the parents often tire of waiting. Andrews, Domankos, Torre-Rodriquez, and Bembenista [22] feel that, while spontaneous involution is seen in a large percentage of hemangioma simplex cases, it is best to treat the larger facial lesions and the smaller eyelid, ear, lip, and nostril hemangiomata because of the likelihood of ulceration should they fail to regress. They feel that all cavernous hemangiomata should be treated. Their choice of treatment is radium therapy.

Bajares and Grom [23] report a case wherein a racemose aneurysm involving the entire upper eyelid and superior orbital region had developed over a seven-year period in a 23-year-old man. There was no lesion present at birth or noted until the age of 16. It apparently started, they say, as a capillary hemangioma on the eyelid. The lesion was diagnosed clinically and by arteriography. The article does not give the treatment or outcome of this serious problem in this case.

Entropion, Ectropion, and Lagophthalmos.

The treatment of trachomatous entropion has not been much of a problem in ophthalmology in this country during recent years, but it continues to be a major problem in trachoma centers. A new method of tarsectomy through a skin approach is reported by Pratt-Johnson.[24] He makes an incision parallel to the lid margin and down to the anterior surface of the tarsus. Through this incision he does a tarsectomy. He then sutures the conjunctiva to the lid margin with a continuous key-pattern suture. A similar suture is used to close the skin, this suture incorporating the levator muscle. He reports good results in 100 cases but states that his follow-up was only a maximum of six weeks.

Kahán and Vén [25] do not approve of tarsectomy. They feel that the shrunken conjunctiva tends to pull the lid margin in, reproducing the entropion, and also tends to produce lagophthalmos. It creates a type of blepharochalasis by shortening the posterior layers of the lid. They surgically lift the conjunctiva from the face of the tarsus, allowing it to retract toward the fornix. The uncovered area of the tarsus is then covered with a mucosal graft taken from the lip. This operation was successful in 29 of 30 cases.

Grafts of various epithelial strips to a groove in the lid margin are not new. The use of a strip of skin from the upper lid is recommended by Drozdowska.[26] It is placed in an incision 2 to 3 mm. deep made along the gray line. He reports 20 successes and 1 failure. Skin is plentiful, but so is mucosa in the required amounts. I can see no advantage in the use of skin and can see some disadvantages.

I should like to recall attention to an entire issue of the *International Review of Trachoma* for 1956, which dealt with the surgical correction of trachomatous entropion. Besnainou [27] gives careful descriptions of most of the operations which are being used. Variations of them will continue to appear. It is hard to visualize radical innovations. Das, Nirankari, and Maudgal [28] appear to have developed one such innovation, however. A strip of skin and muscle is removed anterior to the tarsal plate. Through this incision the tarsal plate is split into two layers. The anterior layer is preserved, a hinge being placed superiorly. The anterior layer of tarsus is turned upward and sutured beneath the skin and muscle layer. This exerts a hinge effect, everting the lid margin. Words cannot describe it. A review of the diagrams is necessary. The operation was completely successful in 78 of 81 cases when it was used as a primary procedure. Of 31 secondary operations, 28 were successfully completed by this technique. Six- to 24-month follow-ups were obtained.

Senile ectropion is believed by Semeraro [29] to be caused by a "new-formed" tissue interposing itself between the skin and orbicularis of the lower eyelid. He feels that excision of this foreign material (at least, foreign to the eyelid) will result in a cure of the ectropion. This is a new concept and one which I do not expect will be widely accepted.

Paralytic ectropion caused by permanent facial palsy is treated by a shortening of the orbicularis muscle in the region of the inner canthus by Németh.[30] This is a difficult problem which cannot be solved by the usual ectropion surgery. I do not feel that the paralyzed orbicularis fibers can be counted upon to give prolonged elevation to the lid unless aided by canthoplasty, usually at both the inner and outer canthi. Ambos [31] (following experimentation) plans to treat lagophthalmos by implanting magnetic implants into both the upper and the lower lids. What will they think of next?

Reconstructive Surgery.—In a discussion of cicatricial ectropion, Blodi and Huffman [32] state that thin split-thickness grafts are the method of choice in correcting cicatricial ectropion of the upper eyelid. They feel that the skin should be taken from the inner aspect of the upper arm. An overcorrection is said to be mandatory because of the tendency of the graft to shrink. In the lower lid they feel that full thickness is all right, as its lack of suppleness is not as important. Here less shrinkage is likely and less overcorrection is necessary. I cannot agree that split thickness is ever as good as a properly obtained and placed full-thickness graft in either lid. Full-thickness grafts often can defy detection. I have yet to see a split-thickness graft from the arm or elsewhere that did not look like foreign skin, either because of color or texture or both. Blodi and Huffman do not feel that lid adhesions are of much importance when split skin is correctly placed; again a point of question.

Sherman [33] does not feel that the Esser epithelial inlay or the Gillies type of epithelial outlay are applicable to the eyelids. He says that they are deforming and may lead to a temporary increase in ectropion in the early postoperative period, thereby endangering the cornea. His article repeats some of the general principles of eyelid surgery and illustrates them with cases.

What seem to me to be some new ideas on skin grafting were brought out by Greeley and Curtin.[34] If capillary bleeding cannot be controlled in a graft site in a fresh surgical wound, they do not hesitate to control it by sterile pressure dressings over the area for a day or two before grafting. If a radiation lesion is the site a longer delay to foster

granulations may be desirable. They "bank" excess skin for a few days or replace it on the donor site for use in case some of the graft fails to take. They do not hesitate to examine grafts in 24 hours if they suspect complications. Evacuation of blood or serum and the reapplication of pressure may save a graft. How do they know which ones to look at early? They "pep up" a sluggish graft with wet boric acid dressings. These are mildly astringent and antiseptic. These points apply, for the most part, to larger grafts than are used in eyelid work, but they are nevertheless interesting and may pertain in some respects in some cases.

The results in eyelid surgery involving the lid margin are better if the excision lines are parallel than if the usual V excision is used. O'Connor, McGregor, and Saffier[35] recommend a block-V type excision with parallel lines at the margin and a V at the base.

A plea for immediate repair of lid lacerations is made by Ruedemann.[36] Since confusing edema results very rapidly after eyelid injury, repair with careful realignment of the deep parts is easier the earlier it is done. Depressed fractures must be ruled out by x-ray, as the edema tends to mask them.

If early repair is not possible, Hartman[37] advises that a delay of at least three months, and often more, be allowed before reconstruction is attempted. Deep cicatricial tissue can be softened with deep massage, and any possible resorption should be allowed to occur before late repair is done.

Spaeth[38] discusses the treatment of depressed and adherent scars. He says that these are caused by faults in primary closure and/or infection. In their repair careful approximation of the deep tissues before skin flaps are sutured is necessary. Replacement of subepithelial tissues with fascia lata, cartilage, etc. may be effective in filling the depression. These must be covered by a closed layer of subepithelial tissue beneath the skin. Spaeth makes one statement which we hear often and with which some of us are not in complete agreement. He says, "All of the scar must be resected no matter how deeply it may have penetrated or how extensively it may have spread." I was glad to see Smith's discussion of Spaeth's paper. He says that at times it is advantageous to leave scar tissue in a wound for the purpose of building up a depression. Excessive excision of scar may lead to further depression of the surface. Superficial tissue can be satisfactorily advanced over the scar tissue. I have seen defects far worse than the original created by the reckless excision of scar tissue and have probably created my share of them by following the scar excision edict. Scar tissue differs considerably from cancer tissue.

Many ophthalmic plastic surgeons do eyelash grafts. Some of them occasionally obtain a satisfactory result; I have not. Lake[39] reminds us of the feasibility of cosmetic tattooing for various defects, including the imitating of eyebrows and hair stubble. While he does not mention eyelashes, I have found tattooing to be simply done and very effective in this regard. Caution must be used in the use of black pigment, as it tends to take on a bluish tint under the skin. Shades of brown usually turn out all right, and, while they may fade, they are easily replaced in a matter of minutes every few years.

Lacrimal Apparatus

Treatment of Xerophthalmia.—Two years ago I reviewed a paper by Loa[40] concerning the transplantation of the parotid duct for total xerophthalmia. It was an article in the *Chinese Medical Journal.* The operation was that of Filatov, described in 1950. The operation was not described in any of the usually available journals in this country until 1957, when Bennett and Bailey[41,42] reported upon it. They successfully transplanted the parotid duct into the conjunctival sac in four dogs and then perfected their technique in human anatomy by cadaver surgery. They report on the use

of the procedure on a patient with total xerophthalmia and corneal ulcers following an exfoliative dermatitis. We do not see many cases where this procedure is necessary. Trachoma, which causes the majority of cases, is rare here. Keratitis sicca is not severe enough to justify its use. The availability of a good reference is a valued addition to our literature should the necessity for its use occur.

A three-year postoperative follow-up on a patient with transplantation of Stensen's duct is reported by Segal.[43] He found that the parotid secretion became more like lacrimal secretion in that it began to contain glucose and sodium chloride. He says that the operation will prevent progression of xerophthalmic lesions, even if it does not improve or cure them.

Problems in Lacrimal Obstruction.—There has been little of note regarding polyethylene intubation during the past year. This in itself is a sign of progress. El-Gammel[44] reports on the use of polyethylene reconstruction of the Callahan type where epiphora cannot be relieved by the usual procedures. A tube with a 1 mm. lumen is placed between the inferior fornix at the inner canthus and the nasal cavity in the region of the anterior tip of the middle meatus. The tube is attached to the medial canthal ligament with a stitch. Four cases were treated successfully.

Postirradiation stenosis of the canaliculi is the subject of a paper by Veirs.[45] He has found that a short piece of polyethylene tubing can be permanently sutured into the common canaliculus to relieve stenosis at that point. A more extensive stenosis can sometimes be opened by the use of a longer tube. If it is of fairly recent origin and if a probe can be easily passed through it, the result is more apt to be satisfactory.

Jonkers, Leffertstra, and Rademakers[46] treated 24 cases of nasolacrimal duct stenosis with the old Vitallium tubes. Seven of these extruded spontaneously, and one had to be removed surgically. Of the remaining sixteen, eight were relatively successful and eight required dacryocystorhinostomy.

An article which goes back to 1955, on the treatment of dacryocystitis with streptokinase and streptodornase (Varidase), warrants comment. Agarwal and Bhar[47] believe that there are three stages in the development of dacryocystitis; the stage of edema and infiltration, the stage of beginning fibrosis, and the stage of complete fibrosis. In Stages 1 and 2 they feel that Varidase is useful. They irrigate with penicillin for four days to clear the infection and then instill 2,000 units of streptokinase and 500 units of streptodornase daily for several days. Thirty-three per cent showed canalization and abatement of symptoms for six months or more. Twenty-five per cent developed ultimate relapse after initial relief. Forty-two per cent, mostly in Stage 3, showed no response.

Another nonsurgical attack on chronic dacryocystitis is reported by Weiner.[48] He was able to avoid surgery in about 50% of cases by the following treatment. After passage of a No. 3 Bowman probe into the nose, he instilled 0.5 cc. of neomycin and cortisone ophthalmic ointment into the tear sac. This was warmed and instilled through a lacrimal irrigating set-up. He felt that it prevented closure of the stricture and permitted epithelization. The treatment could be repeated in about seven days, and as many as six treatments were required in some cases to obtain the 50% success rate.

The preoperative use of antibiotics when dacryocystorhinostomy is contemplated is practiced by many surgeons. Belmonte[49] reminds us that the success of this operation depends to a large extent upon good coaptation between the lacrimal and nasal mucosa. Most of us are aware of the fact that our results are better when the sac is dilated, as this anastomosis is more satisfactorily accomplished. Belmonte says that while the use of antibiotics improves the clinical picture of dacryocystitis, it results in shrinkage of the sac and therefore re-

duces the chance of surgical success from dacryocystorhinostomy.

There appears to be little new in the technique of dacryocystorhinostomy. Sachsenweger[50] sutures a rubber drain into the newly created duct. He holds it in place for 6 to 10 days with two nylon sutures, one through the canaliculus and one through the nose. A similar operation is reported by McLoone.[51] He uses a No. 12 F. Robertson rubber catheter anchored to the tear sac wall. He removes it in one week. Charchenko[52] uses a tampon of gauze soaked in sterile oil and sprinkled with penicillin and sulfonamide powder. It is left in place only for two days. He reports 99.4% success in 315 operations. He confirmed his results with the fluorescein test. Bonaccolto[53] presents a novel way of holding a polyethylene catheter in the dacryocystorhinostomy opening. A catheter composed of two parts, having diameters to fit the canaliculus and the opening, is constructed. It is held in place by tension on the canalicular side, the small end of the catheter emerging through the punctum and being fixed to the brow. In the usual case none of these are as good as accurate stuturing of the tear sac mucosa to the nasal mucosa. When this is impossible, these devices have a place.

Guenther[54] studied six cases of failure in dacryocystorhinostomy. Five of the failures were thought to be due to too small a bony opening and one to a faulty position.

A reconstruction of the tear sac is reported by Eptein.[55] He wrapped a piece of buccal mucosa around an absorbable gelatin sponge (Gelfoam) matrix and sutured the free edges. He implanted this into the normal position of a missing tear sac, anastomosing it to the common canaliculus. Two months later, an opening was made into the nose and a dacryocystorhinostomy was successfully done.

Epiphora due to eversion of the lower punctum was treated by a surgical inversion of the punctum by Németh.[56] He did a "Z-like plasty," transposing the punctum-containing tissue with a conjunctival flap.

It is thought by many that movement of the upper eyelid is important in the flow of tears from the eye to the lacrimal duct. Hanney[57] studied 25 patients who had limitation of movement of the upper lid following surgery for ptosis. He found that in 22 of these spontaneous patency was present and concluded that upper-lid movement was of less importance than is generally thought.

An instrument for examination of the nasal opening of the nasolacrimal duct is described by Kuribayashi.[58] It is a 3×6 mm. mirror attached to the end of a probe. With it he has found much variation in the shape and action of Hasner's valve. This valve seems to prevent the back flow of nasal secretion in most cases.

Sjögren's Syndrome.—In a study of tears by filter-paper electrophoresis Erickson, Hatlen, and Berg[59] found that the tear proteins (albumin, globulin, and lysozyme) were essential to a viscous tear film. As the rate of tear flow decreases in Sjögren's syndrome, the first protein to decrease is lysozyme. A comparative increase in albumin occurs, and this is coincident with the complaint of burning and discomfort. Then all three lacrimal proteins begin to disappear, and the sicca pattern results. McEwen, Kimura, and Feeney[60] studied the fractions of tears secreted by the lacrimal glands, the accessory glands, and the goblet cells. They found that lysozyme and tear albumin were secreted by the lacrimal glands.

Weber[61] suggests that keratoconjunctivitis sicca might be caused by a medullary lesion in the region of the salivatorius pontis, affecting the parasympathetic nuclei. The nature of this lesion might be dysplastic, inflammatory, circulatory, toxic, or tumorous. Gáll[62] feels that the production of tears and the function of the gonads are interrelated phenomena. He feels that there might be a neural factor also, in that "diminished neural tone" is present in keratoconjunctivitis sicca patients. It is present in many of us who do not have keratoconjunctivitis sicca.

Biopsy of the lacrimal gland was done in three cases of Sjögren's syndrome by Funatsu and Eguchi.[63] In two there was atrophy of the gland cells, and in one there was infiltration with small round cells.

Miscellaneous.—A case of acute dacryoadenitis seen during the course of a case of mumps is reported by Krishna and Lyda.[64] Suppuration developed, the exudate being milky in character. It was negative bacteriologically. Mumps being as common as it is, it seems odd that ophthalmic complications are not more frequently seen.

Of 20 caruncles obtained at autopsy Nover[65] found serous glandular elements in 8. Aberrant lacrimal gland tissue is not terribly unusual, but one does not think of it as being a component of the caruncle.

Conjunctiva

Trachoma.—The most momentous contributions to the conjunctival literature concern the isolation and cultivation of the trachoma virus. This has been attempted for many years, but it has only been during the past year that apparent success has been attained. T'ang, Chang, Huang, and Wang[66] isolated three strains of what seemed to be trachoma virus, using chick embryos as the medium. This virus, when inoculated in the conjunctival sac of rhesus monkeys, produced a follicular conjunctivitis, which yielded inclusion bodies in one instance. This presumptive evidence is given credence by the work of Collier and Sowa.[67] They confirm the laboratory aspect of the work of T'ang et al. by carefully controlled research with use of a virus isolated from an active case of trachoma in Gambia. The final proof required reproduction of the disease by inoculation of a human volunteer. One might criticize their choice of the volunteer, as he was a patient who had had a bilateral enucleation. However, one can understand why a normal volunteer might be a little hard to find. At any rate, both conjunctival sockets were inoculated with material from the eighth egg passage. The right socket remained more or less negative throughout the observation period. In the left socket hyperemia and discomfort developed on the second day. This increased until by the 14th day a fairly profuse discharge associated with a papillary hypertrophy had developed. By three weeks the conjunctiva appeared granular with numerous small opaque foci. The preauricular gland became tender at this stage. By one month the entire conjunctiva had become rather densely infiltrated. At the time of the report the condition had not gone on through the further stages of trachoma, and, of course, these will be modified by the absence of the globe.

Laboratory studies were done at numerous stages. Elementary bodies were identified in the scrapings by the 7th day but were not seen after the 14th day. A few initial bodies were seen by the 7th day and became very numerous by the 21st day. On the 14th day material from this socket was inoculated into three chick embryos. In one of them a yolk-sac smear showed numerous elementary bodies identical with those found in the inoculation material.

A skeptical person might hesitate to accept the above as acceptable proof of the successful cultivation of the trachoma virus. Similar attempts with egg-embryo culture have been unsuccessfully tried by many others in the past. The disease produced in the rhesus monkeys and in the sockets of the volunteer could be questioned as to its being true trachoma. I understand that Collier and Sowa have now made some inoculations on more suitable volunteers. I believe that most of us will agree that these reports show preliminary success in the long-sought proof of the virus nature of trachoma. Undoubtedly further reports will be coming from these investigators, and attempts to duplicate their works in other laboratories will be reported. Perhaps within the next year or two this age-old problem will be settled.

One more bit of evidence along the above line is reported by Fujiyama.[68] He was

able to demonstrate serial passage of what he considered to be the trachoma virus, using the chorioallantoic membrane of fertile chick eggs as the culture medium.

The similarity between the trachoma virus, the psittacosis virus, and the lymphogranuloma venereum virus are well known. Bietti, Babudieri, and Pannarale [69] state that positive complement-fixation tests are seldom obtained with the latter two when serum from trachomatous patients is used. They feel that this lack of response is due to the fact that trachoma is a localized disease and only a small amount of antibody can be expected in the serum. However, they strengthened the evidence of antigenic similarity by preparing an antigen from trachoma material, testing it with the serum of persons suffering from lymphogranuloma venereum and psittacosis, and obtaining positive complement-fixation reactions.

A trachoma manual by Thygeson [70] published by the United States Public Health Service should be available to all ophthalmologists. Thygeson states that due to the virtual disappearance of trachoma from the white population of the United States a resident may complete his entire training without having seen a case of active trachoma. The manual furnishes a good discussion of trachoma classification and fundamentals of diagnosis and treatment and contains an excellent set of black-and-white and colored photographs of the various stages of the disease. Thygeson says that mother-to-child transmission is the principal epidemiologic factor and that transmission from school-child to school-child is responsible for only a minority of cases.

A well-worth-while fundamental article on trachoma by Mori [71] has appeared. He describes the technique of taking and staining smears and the identification of inclusion bodies, etc. After so many electron-microscope reports it is nice to see that interest in the light microscope still exists. Mori has found azurophilic reticular inclusion bodies in early epidemic keratoconjunctivitis and offers this as further evidence of the virus nature of this disease.

A critical review of the evidence for the virus nature of trachoma and a discussion of the properties of the virus of trachoma is found in the *International Review of Trachoma* for 1958. It is written in French and in English by Thygeson and Nataf.[72] The mechanism of action of the sulfonamides and the antibiotics is discussed. It is the feeling of the authors that no race is immune and that regional variation can best be explained on the basis of differences in the age of onset and the frequency and type of secondary bacterial or viral infection.

Aoki [73] says that in Japan acute trachoma can be either pure or associated with an overlying Koch-Weeks bacillus infection. Several types of infection can result depending upon the conditions. Tsutsui [74] feels that the opinion of the expert committee on trachoma of the World Health Organization that trachoma has an insidious onset is not correct, at least in Japan. Many Japanese authorities feel that the onset is usually acute or subacute in both experimental and natural trachomatous infection. Tsutsui feels that the classification should be reviewed in regard to the early stages of the disease. Kunitomo, Asakage, Mori, Miyata, and Dake [75] say that in infants trachomatous onset is always acute or subacute and never insidious. They say that the lower lids are more severely involved than are the upper lids in these infants. Sezer [76] says that the inflammatory reaction of trachoma has an early polymorphonuclear and a later reticuloendothelial reaction and is therefore a mixed inflammation. In a cytologic study Nakajima and Otaki [77] found the same cellular response to trachoma infection. They also found a slight leukocytosis of short duration in the acute stage and an eosinophilia and lymphocytosis in Stage III. In Stage III they found a slight decrease in the albumin fraction and a slight increase in β- and γ-globulin in the serum protein of the blood.

Yuge [78] is of the opinion that chronic trachoma may be an allergic reaction in the lymphatic tissues of the conjunctiva following the acute sensitizing disease. The fact that it relapses and subsides without treatment is accounted for by this concept. I suppose that the eosinophilia mentioned above would add some credence to the idea of "trachoma allergy."

Trachoma dubium is a follicular conjunctivitis which is seen in the Missouri "trachoma belt." It affects mostly children and has often been diagnosed as a mild or incipient form of trachoma. It is characterized by a red velvety papillary hypertrophy of the conjunctiva with a follicular engorgement of the submucosa. There is haziness and loss of transparency of the conjunctiva. There is no evidence of pannus formation. Cady [79] studied 42 cases and found no difference in the course between the untreated cases and those given trachoma treatment. There were no inclusion bodies found in the smears. Cady feels that so-called trachoma dubium is not related to trachoma.

The provocative effect of cortisone on clinically healed trachoma is reported by Mohsenine and Darougar [80] and by Dérer, Klomešová, and Elischerová.[81] The former authors found recurrence of symptoms and reappearance of inclusion bodies in most cases. The latter authors had only 2 recurrences in 34 clinically healed cases and felt that the cortisone test was a reliable gauge as to the presence of a real cure. They also felt that it might be useful in the differential diagnosis of doubtful conjunctivitis cases.

There were four recent articles [82-85] on the epidemiology of trachoma. Alimuddin [82] says that in East Pakistan the incidence of the disease is only 1% to 2%, while in West Pakistan it is 66%. He attributes this to better personal hygiene in the East and to better climatic conditions and relative freedom from insect carriers. Siniscal [83] reports on the incidence in the United States and notes a decline in both the Indian and the white populations. Owing to control and treatment programs the cases seen now are mostly those of complications from active cases of 20 to 50 years ago. Rohrschneider [84] found a very low incidence among Germans displaced to trachomatous areas because of World War II. Also, he noted a low incidence of infection spreading from trachomatous persons displaced into Germany. He attributes this to the high standard of personal hygiene observed by Germans and also to favorable climatic conditions in Germany. Voinova [85] states that in the U. S. S. R. the incidence of trachoma has been reduced by intensive case-finding and treatment programs to 6.7% of eye patients. These are mostly Stage III cases. Only two to three months of treatment is necessary at this time.

The treatment of trachoma has, for the most part, not changed. A few articles on this phase of the disease merit review. Bietti [86] states that treatment varies from that of bacterial disease in that it must be continued for periods of three to five months. Of the antibiotics Bietti says that penicillin is the least effective and that the tetracyclines are the most effective. Bietti and Lanzieri [87] report on the use of a slowly eliminated sulfonamide preparation (sulphamethoxypyridiazine, or Kynex) in trachoma treatment. They treated 57 patients with Stage II trachoma and found 70% cured at the end of three months. The medication is taken orally once daily. There were no side-effects, and there was no intolerance to the drug. They feel that it is a good medium for mass treatment. Dyudina [88] reports what he says is an entirely new treatment for trachoma. He combined a sulfonamide (Aethazolum) with a hyaluronidase preparation locally and gave the sulfonamide systemically. He says that there are no side-effects, but he suggests that intestinal parasites and pulmonary tuberculosis be excluded before the treatment is begun. He says that over half of the Stage III patients showed marked improvement. Araez-Pacheco [89] feels that late stages of trachoma respond poorly to

sulfonamide and antibiotics because the medications do not reach the subconjunctival tissues. He feels that we need to revive some of the old mechanical methods of breaking down the trachoma follicles in treating the more advanced cases.

Adenovirus Eye Infections.—While the volume of literature on trachoma never seems to decline, there has been a dramatic decline in the number of adenovirus articles during the past year. New findings and a revival will be welcome in a year or two—or three.

Hanna, Jawetz, Mitsui, Thygeson, Kimura, and Nicholas [90] state that up to now they have not seen a patient with typical epidemic keratoconjunctivitis whose serum did not possess antibodies to the herpes simplex virus. They feel that both herpes simplex and adenovirus Type 8 may be necessary to produce full-blown epidemic keratoconjunctivitis with corneal opacities.

In an epidemic of epidemic keratoconjunctivitis in a Japanese city Tanaka [91] found Type 8 adenovirus-neutralizing antibodies in most of the cases. In one typical case, Type 7 adenovirus was recovered from the conjunctival specimens and Type 7 antibodies were found in the serum. She concludes that Type 7 adenovirus is one cause of epidemic keratoconjunctivitis. Kobayashi and Hirota [92] isolated a strain of Type 11 adenovirus from a case of epidemic keratoconjunctivitis. It produced the typical disease in a human volunteer. Bennett, Law, Hamilton, and MacDonald [93] isolated three strains of Type 8 adenovirus, two strains of Type 1, and one strain each of Type 7 and Type 11 in 76 viral conjunctivitis cases. Only Type 8 was found in those cases with corneal opacities.

The diagnosis of epidemic keratoconjunctivitis has received more attention than has its treatment. Tosch [94] reports that if treatment with hydrocortisone and neomycin ointment is started before the fourth day of the disease corneal opacities are rarely seen. Without this treatment 70% develop these opacities.

An article by Thygeson [95] on the various virus diseases which affect the eye and its adnexa appeared as part of the virus disease symposium at the 1957 American Academy of Ophthalmology and Otolaryngology meeting. It does not lend itself to abstracting and does not contain much new information, but it is quite comprehensive and should be read by all of us.

Other Infections.—On the failure of silver nitrate in the prophylaxis of gonococcal ophthalmia neonatorum, Pearson [96] reports 40 cases in 67,200 live births. Nearly half of these were in premature babies, and Pearson felt that the failures were due to poor resistance to infection in these infants. Harris [97] compared penicillin ointment to silver nitrate in 2,424 babies where the drugs were used in alternate cases for prophylaxis. The results were comparable, there being 14 severe and 27 milder conjunctival reactions with silver nitrate as compared to 11 severe and 22 milder reactions with penicillin.

Three cases of unilateral conjunctivitis and canaliculitis of the type frequently seen with Streptothrix but found to be due to fusiform bacilli and spirochetes are reported by Burns, Macnie, Pfeiffer, and Locatcher-Khorazo.[98] They feel that irrigation with penicillin was the best treatment.

In southern Morocco Ponghis [99] reports that the incidence of acute and subacute conjunctivitis fell dramatically in 24 villages when the fly population was reduced by the use of insecticides.

Hallett and Leopold [100] report erythromycin ophthalmic ointment to be effective in the treatment of most cases of bacterial extraocular infection. They found, however, 4.7% allergies, 4% being severe enough to necessitate cessation of the treatment. In an in vitro study Leibold and Suie [101] found sulfacetamide effective in 88 out of 91 ocular strains of staphylococci. The most effective ranges were 7.5% to 15%. This study supports the excellent clinical results obtained with this drug. It

has a definite place in the treatment of staphylococcal infections which are becoming more and more resistant to the antibiotics.

In a group of rats and rabbits fed on a pyridoxine(vitamin B_6)-deficient diet Irinoda and Mikami [102] found that angular blepharoconjunctivitis developed. They found also that these animals were more susceptible to experimental infection with the Morax-Axenfeld bacillus than were normal controls. They found that the urine of patients with angular blepharoconjunctivitis contained less pyridoxine than did that of controls. From these findings they conclude that angular blepharoconjunctivitis is chiefly a pyridoxine-deficiency manifestation and that Morax-Axenfeld infection has only a secondary significance.

Pterygium.—The pathogenesis of pterygium is discussed by Kubik.[103] From a study of over 100 cases he is of the opinion that long-standing irritation of the bulbar conjunctiva and cornea by irregular prominences on the upper and lower eyelids may be a causative factor. He lists Meibomian concretions, inflammatory granulomas, hairs of the caruncle, lid margin irregularities, and prominent lacrimal papillae as causes. He feels that removal of these is necessary if recurrences are to be prevented. The frequency of the above lesions and the rarity of associated pterygia in my experience would make me doubt a connection between them.

A case of congenital pterygium was reported by Malhotra.[104] The growth was noted at birth and increased in size between ages 2 and 4. The author suggests a disorder of the corneal nerves leading to degeneration of the overlying layers of the cornea as the cause. The conjunctival growth could be a reaction attempting to fill in the defect resulting in the cornea.

Mims [105] believes that pterygium starts when a small area of Bowman's membrane and the underlying stroma is affected for some reason by a degenerative process. A vascular connective tissue proliferates into the defect, and corneal epithelium is replaced by a conjunctival type of tissue. The fibroblasts become adult, and they contract, drawing the conjunctiva toward the head of the lesion. Mims excises the involved tissue, including the superficial corneal lamellae in the area. He sutures the conjunctiva to the sclera. He gives radiation in three or four days and again in two weeks. In 42 cases, with a two-year follow-up, he has had no recurrences.

A high recurrence rate was reported in the treatment of pterygium by an operation similar to the above but without radiation. Seventy-four per cent recurred within a year, according to Fulgosi and Frank.[106] They feel that radiation would reduce this rate considerably.

Escapini [107] totally excises the pterygium along with the subconjunctival tissue. He then covers the defect, except for an area of sclera near the limbus, with healthy conjunctiva. He does not feel that steroids help to prevent recurrences. If there is no tendency to recur within one month Escapini feels that there will be none. He had 2 recurrences in 180 primary cases and 2 recurrences in 4 recurrent cases by the use of this technique. His observation period was from 2 to 12 months.

Complete excision of the pterygium and covering of the defect with a free conjunctival graft taken from the superior fornix of the same eye is recommended by Ebadi.[108]

A new concept and probably the only new one to appear during the past year is presented by Newton.[109] He noted no pterygium formation in many cases of cataract surgery and reasoned that perhaps the corneal incision somehow inhibited vascularization. In 10 operations for recurrent pterygium by transplantation he combined the procedure with a limbal incision into the anterior chamber. He closed this with one or two 000000 chromic absorbable surgical (gut) sutures. There were no true recurrences after a 3- to 12-month follow-up. He later made the corneal incision

about two-thirds of the thickness of the cornea and hence eliminated the dangers of a paracentesis. This simple addition to any of the pterygium operations may be the answer to the annoying recurrence problem. Further reports will be awaited with much interest.

Pigmented Tumors of the Conjunctiva.

Several articles have appeared which bring out the unpredictable course of melanotic tumors. Reese and Straatsma [110] have found that precancerous melanosis may remain unchanged for an indefinite period, may undergo temporary or permanent regression, or may progress insidiously and rapidly to a frankly malignant state. They feel that precancerous melanosis can be diagnosed by biopsy and observed for evidence of progression. While radiation may decrease the pigmentation, its ultimate effectiveness is unknown. The active precancerous stage requires exenteration of the orbit if complete removal by local excision is not feasible. Cancerous melanosis requires exenteration if it is diffuse and if there is no evidence of metastasis.

Lewis and Zimmmerman [111] state that while many malignant melanomas of the bulbar conjunctiva are successfully treated by local excision, in view of our present state of ignorance and our inability to predict which tumors will recur or metastasize, it may be best to follow Reese's advice and exenterate the orbit. However, they feel that a reevaluation of the surgical management of these tumors is in order. Perhaps long-term follow-up would show that simple excision, repeated if necessary, may be as adequate as exenteration.

François, Rabaey, and Evens [112,113] emphasize the difficulties in clinical and pathological interpretation of malignant melanotic conjunctival tumors. They feel that radical excision of the tumor after a delimiting diathermy coagulation of the neighboring zone will give the best results. If the lesion is diffuse exenteration is indicated.

The use of diathermic coagulation to the entire lesion is advocated by Dvorak.[114] He says that it can be repeated if necessary. It tends to prevent dissemination and can preserve a seeing eye.

Six local excisions of an anaplastic malignant melanoma of the conjunctiva over a 13-year period were reported by Irvine.[115] Each time the lesion was widely excised the margins were found to be normal, and each time it recurred. Finally an exenteration was done. There was no sign of metastasis. The lesion was microscopically very malignant and clinically comparatively benign.

A conjunctival melanotic lesion of 23-years' standing was excised and found to be a malignant melanoma by Blake and Fasanella.[116] P^{32} studies were useful in the preoperative diagnosis. Gaipa [117] removed a benign congenital nevus from the limbus and reports that a malignant melanoma formed at the site of excision 15 months later.

Conjunctival Allergy.—An excellent article on allergic diseases of the eye was written by Leopold and Leopold.[118] They include a discussion of eyelid and conjunctival allergic conditions. Treatment consists of either elimination of the allergen or desensitization to it, if this is possible. Otherwise, the treatment is palliative, with epinephrine, antihistamines, or steroids. There are some reported sensitivities to the antihistamines. Their popularity seems to be declining, at least insofar as local use is concerned.

Theodore's [119] article on the treatment of ocular allergy is also excellent. He divides ocular allergy into three groups: (1) an immediate anaphylactic response to pollens, inhalants, animal proteins, or foods; (2) delayed response, 24 to 48 hours, due to a microbial infection, and (3) a more delayed response due to contact from drugs, cosmetics, and other chemical products. He states that all eye allergies except vernal catarrh can be included in one of these groups. His ideas on treatment are similar to those of Leopold and Leopold. He feels

that the local use of antihistamines is of little if any therapeutic value.

Abrahamson and Abrahamson [120] report on the use of a combination of 0.3% chlortrimeton gluconate and 0.2% prednisolone acetate called Metreton. They feel that the local use of the combination is better than the local use of either alone.

In treating vernal conjunctivitis, di Ferdinando and Gattini [121] feel that their best results were obtained when local applications of cortisone were combined with intradermal corticotropin (ACTH).

When the more conservative treatment of vernal catarrh has failed to give relief, Ebenius, Larsson, Cederquist, and Christiansson [122] resort to contact x-ray therapy or radiation with radon. In their series of 20 eyes, 18 showed complete subjective and objective cure, while 2 showed improvement. Their follow-up was from 2 to 11 years. They report no complications.

An interesting case of vernal conjunctivitis is reported by Weber and Strohbusch.[123] In a 13-year-old boy a typical severe spring catarrh affected only one eye. The diagnosis was verified histologically. The disease was resistant to all treatment. They suggest that the unilaterality could best be explained by the influence of local factors. Angioneurotic hyperemia or passive hyperemia due to tissue pressure, preexistent scars, or lymphostasis are mentioned.

Injuries.—Molten metal burns are not seen frequently, but they are apt to lead to serious sequellae. Callahan and McKerricher [124] advise early treatment by irrigations and the local use of steroids. They feel that the frequent separation of adhesions between the globe and the lids is useless and stimulates more cicatrization. They state that conformers are without value except after cicatrization is completed and surgically removed and grafting is done. They prefer genital mucosa when large grafts are needed. I am afraid that I will continue to separate adhesions, use conformers, and use buccal mucosa and such bits of conjunctiva as are available.

The use of peritoneum as a mucus membrane substitute has been used by many with varying degrees of success. A new idea is the use of "banked" peritoneum. Malhotra [125] removes the peritoneal lining of hernial sacs which are easily obtained in most hospitals. They can be stored in normal saline at 4 C for up to 18 days. He reports good results from the use of this tissue.

Conjunctival Vessels.—Two articles concerning aneurysms of the conjunctival vessels in diabetics have appeared. Riedl [126] compares the conjunctival vessels in a group of diabetics with those of a group of normal subjects. Aneurysms were found in 47% of the diabetics and in 18.8% of the nondiabetics. There was no correlation between the presence of conjunctival aneurysms and retinopathy. He feels that the presence of conjunctival aneurysms is suggestive but not diagnostic of diabetes. Meunier and Zanen [127] found fusiform or saccular aneurysms in 35% and berry-shaped aneurysms in 15% of 60 diabetics. Seven of the nine diabetics with berry-shaped aneurysms also had retinopathy.

A study of the bulbar-conjunctival vascular bed in diabetic children was made by Ditzel and Duckers.[128] They found two types of changes. The first is a generalized distention of the venules occasionally associated with fusiform dilatations. There is an associated slowing-down of the blood flow in the capillaries and the smaller venules and often areas of localized edema. The second is a generalized constriction of all of the vascular elements with a resulting ischemia of the tissues. The direct A-V communications open, and the red blood cells aggregate in clumps. The first type is more frequent. These conjunctival vascular changes are commoner in the cases of long duration.

A new syndrome in which the conjunctival vessels are involved is described by Boder and Sedgwick.[129] It is called familial

ataxia-telangiectasia syndrome. It is characterized by progressive cerebellar ataxia, telangiectasia formation in the bulbar conjunctiva and butterfly area of the face, and susceptibility to sinopulmonary infection. The telangiectasia formation may spread to the hard and soft palate, the neck, the anticubital and the popliteal spaces, and the dorsum of the hands and feet. The conjunctival changes are seen in the horizontally placed vessels. They fade near the limbus. They give the eyes a pink appearance. Pathologically enlarged venules are found in the leptomeninges and white matter of the brain. There are no spinal cord changes.

"E multis paleis paulum fructus collegi."

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News and Comment

ANNOUNCEMENTS

Wills Eye Hospital Annual Clinical Conference.—The Eleventh Annual Clinical Conference of the Wills Eye Hospital Staff and Society of Ex-Residents will be held in Philadelphia at the hospital on Thursday, Friday, and Saturday, Feb. 19-21, 1959. A number of new and attractive features are planned by the committee for this event.

The Arthur J. Bedell Lecture on "Complications Following Cataract Surgery" will be delivered by Dr. Brittain Payne. In addition to individual presentations, color television surgery, and clinical, surgical and research subjects, the scientific program will include special surgical clinics on Thursday.

On Thursday evening, Feb. 19, there will be a scientific meeting of the Ophthalmological Section of the Philadelphia College of Physicians which will be preceded by dinner, and everyone is invited to attend. Dr. Raynald N. Berke will be the guest speaker on the subject of "Surgical Treatment of Blepharoptosis."

The social activities will include an informal reception for all those who attend, on Friday evening, Feb. 20. The Conference will be concluded by a dinner meeting of the Society of Ex-Residents of the hospital.

Research Study Club of Los Angeles Annual Midwinter Convention.—The Research Study Club of Los Angeles will hold its 28th Annual Midwinter Convention in Ophthalmology and Otolaryngology Jan. 26-30, 1959, at The Ambassador Hotel, Los Angeles.

The guest speakers in ophthalmology will be A. Franceschetti, M.D., Professor, Clinique Ophthalmologique, Geneva; Arthur G. DeVoe, M.D., Professor of Ophthalmology, Bellevue Medical Center, New York; Lester T. Jones, M.D., Clinical Professor, University of Oregon, Portland, and Arthur Jampolsky, M.D., Assistant Clinical Professor of Ophthalmology, Stanford School of Medicine, San Francisco. Instruction courses will be taught by Drs. Franceschetti, Jones, and Jampolsky and by Dr. Carrol L. Weeks, Los Angeles.

The guest speakers in otolaryngology will be Francis L. Lederer, M.D., Professor of Otolaryngology, University of Illinois College of Medicine, Chicago; F. Johnson Putney, M.D., Associate Professor of Laryngology and Bronchoesophagology, Jefferson Medical College, Philadelphia; Victor Goodhill, M.D., Clinical Professor of Surgery (Otology), University of Southern California School of Medicine, Los Angeles; Howard P. House, M.D., Professor of Otolaryngology, University of Southern California School of Medicine, Los Angeles; Max Pohlman, M.D., Department of Surgery (Otolaryngology), University of Southern California School of Medicine, Los Angeles, and Joel J. Pressman, M.D., Professor of Surgery, Chief of the Division of Head and Neck Surgery, University of California School of Medicine, Los Angeles. Instruction courses will be taught by Drs. Lederer and Putney and by W. E. Compere Jr., M.D., Los Angeles, Manuel R. Wexler, M.D., Los Angeles, and E. W. Johnson, Ph.D., Instructor in Audiology, Department of Speech, University of Southern California, Los Angeles.

All lectures on ophthalmology and otolaryngology, as well as the instruction courses of both groups, will be held at The Ambassador Hotel during the week of Jan. 26-30. However, registration will begin on Sunday, Jan. 25, at 2 p.m. in the Embassy Room in the main hotel lobby. The lectures and instruction courses will begin Monday, Jan. 26, and continue through Friday, Jan. 30.

This year we were able to secure a special course in cardiac resuscitation, which will be given by William P. Mikkelsen, M.D., who has conducted this course at the University of Southern California for the past several years. This

outstanding course, including laboratory demonstration, will be available for an additional fee of $50 and will be limited to the first 25 applicants.

Motion pictures dealing with ophthalmological and otolaryngological subjects will be presented by Clifford N. Crawford, M.D., and Francis Morris, M.D., respectively.

The round-table luncheons, as in the past, will be the heart of the convention, and members are invited to enter into informal discussion on any topics which concern them. All luncheons are included in the fee for the course.

Thursday evening, Jan. 29, will be the occasion for the banquet of the Los Angeles Society of Ophthalmology and Otolaryngology, which will be held in the famed Cocoanut Grove. All members and their wives are invited to attend.

All applicants must be members in good standing of the American Medical Association in order to become eligible for attendance at the Convention. The fee for the entire course or any part of it is $110. This includes the cost of all round-table luncheons. Make your check payable to Research Study Club and mail to Norman Jesberg, M.D., 500 S. Lucas Ave., Los Angeles 17.

Basic Science Lecture Schedule at Washington Hospital Center.—The Department of Ophthalmology of the Washington Hospital Center is offering a series of lectures on the basic sciences as applied to ophthalmology, to be given on Saturday mornings from 8:00 a.m. until 12:00 noon. These are designed for the resident staff in ophthalmology in preparation for board examinations. All physicians, however, are cordially invited to attend the entire course or the individual lectures they desire. There are no fees for attendance. The lectures are held in the Glaucoma Clinic (Room GA-E-38) on the ground floor of the Washington Hospital Center, 110 Irving St. N. W., Washington 10, D. C.

Dr Boeder will give three evening lectures in addition to his scheduled lectures. Further announcements of addenda will be made during the course.

The schedule of the remaining lectures is as follows:

Feb. 7—Dr. Zimmerman: Pathology—Inflammation.
Dr. Silverstein: Immunochemistry—In Vivo Immunological Reactions (continued from Jan. 31).

Feb. 14—Dr. Zimmerman: Pathology—Experimental Uveitis.
Dr. Silverstein: Immunochemistry—Experimental Ocular Immunology.

Feb. 21—Dr. Zimmerman: Pathology—Granulomatous and Nongranulomatous Uveitis.
Dr. Silverstein: Immunochemistry—Ocular Diseases of Suspected Immunological Orgin.

Feb. 28—Dr. Halbert: Microbiology—Factors Involved in Bacterial Virulence.

March 7—Dr. Halbert: Microbiology—Host Factors Involved in Bacterial Virulence.

March 14—Dr. Halbert: Microbiology—Viruses and Mechanisms of Viral Infections.

March 21—Dr. Halbert: Microbiology—Parasitic and Fungal Infections.

March 28—Dr. Witkop: Genetics—Basic Principles and Medical Genetics.

April 4—Dr. Green: Biochemistry of the Aqueous.

April 11—Dr. Green: Physiology of the Aqueous.

April 18—Dr. Leopold: Pharmacology—Antibiotic Drugs and Steroids.

April 25—Dr. Leopold: Pharmacology—Autonomic Drugs, Etc.

May 2—Dr. Donaldson: Neuroanatomy.

May 9—Dr. Donaldson: Neuroanatomy.

May 16—Dr. Boeder: Optics.

May 23—Dr. Boeder: Optics.

Fight For Sight Awards of National Council to Combat Blindness, Inc.—The Scientific Advisory Committee of the National Council to Combat Blindness, Inc., has announced its 1958-1959 Fight For Sight Awards, totaling $128,214 in grants-in-aid and fellowships allocated to medical colleges, hospitals, and individual investigators for research in ophthalmology and related sciences.

Many of the grants represent initial support by the organization to basic research investigations in ophthalmology; others will provide continued support to projects which have received Council aid in the past.

This action by the Scientific Advisory Committee provides 34 grants-in-aid to medical colleges and hospitals in the United States and abroad and a special award to the New York Academy of Sciences for an International Symposium on Photoreception, in addition to 8 full-time research fellowships, 1 traveling fellowship, and 21 student research fellowships.

Five foreign medical centers share in the grant-in-aid awards. They are General Hospital, México, D. F.; Hadassah University, Department of Ophthalmology, Jerusalem; Kumamoto University Medical School, Japan; Medical Research Council, Institute of Ophthalmology, University of London, England, and Nuffield Laboratory of Ophthalmology, Oxford University, Oxford, England.

Fight For Sight grants-in-aid and full-time research fellowships are generally awarded for a period of one year and may be extended for an additional period with the approval of the Scientific Advisory Committee of the National Council of Combat Blindness, chaired by Charles A. Perera, M.D., Associate Clinical Professor of Ophthalmology, Columbia University College of Physicians and Surgeons.

The Council announces that it is now accepting applications for its 1959-1960 Fight For Sight grants-in-aid, research fellowships, and summer (1959) student fellowships.

The closing date for receipt of completed applications for grants and fellowships has been advanced to March 1, 1959, in order to allow ample time for processing and review. Applications for summer student fellowships will be reviewed in advance of the June meeting of the Scientific Advisory Committee. Appropriate forms may be obtained by addressing the Secretary, National Council to Combat Blindness, Inc., 41 W. 57th St., New York 19.

The Scientific Advisory Committee of the National Council to Combat Blindness, which votes on all awards, now numbers 18, having recently welcomed to its ranks a new member, Frank W. Newell, M.D., Chairman of the Section of Ophthalmology, Department of Surgery, The University of Chicago, The School of Medicine. Other members of the Committee are as follows:

James H. Allen, M.D., Chief, Department of Ophthalmology, Tulane University School of Medicine; Bernard Becker, M.D., Chief, Department of Ophthalmology, Washington University School of Medicine; Alson E. Braley, M.D., Director, Department of Ophthalmology, State University of Iowa, University Hospitals; Frederick Crescitelli, Ph.D., Department of Zoology, University of California; Arthur G. Devoe, M.D., Chief, Department of Ophthalmology, New York University-Bellevue Medical Center; Dan M. Gordon, M.D., Assistant Professor, Department of Ophthalmology, New York Hospital-Cornell Medical Center; Charles Haig, Ph.D., Associate Professor, Department of Physiology and Pharmacology, New York Medical College; Michael J. Hogan, M.D., Director, Francis I. Proctor Foundation, University of California School of Medicine; Peter C. Kronfeld, M.D., Professor, Department of Ophthalmology, University of Illinois College of Medicine; Irving H. Leopold, M.D., Director of Research, Wills Eye Hospital, Philadelphia; A. E. Maumenee, M.D., Director, Department of Ophthalmology, The Johns Hopkins University School of Medicine; Stuart Mudd, M.D., Professor, Department of Microbiology, University of Pennsylvania; Theodore C. Ruch, Ph.D., Chairman, Department of Physiology and Biophysics, University of Washington; Samuel L. Saltzman, M.D., Assistant Professor, Department of Ophthalmology, New York Medical College; Kenneth C. Swan, M.D., Chief, Department of Ophthalmology, University of Oregon; Phillips Thygeson, M.D., Professor of Ophthalmology, University of California School of Medicine.

Following are the 1958-1959 Fight For Sight Awards:

Grants-in-Aid

Investigator	Institution	Project Title	Amount
Adler, Francis H., M.D., and Frayer, William C., M.D. (continuation)	Department of Ophthalmology, Hospital of the University of Pennsylvania, Philadelphia	Study of the Factors Involved in the Proliferation of the Retinal Pigment Epithelium in Disease	$1,000
Alpern, Mathew, Ph.D.	Department of Ophthalmology, University of Michigan Medical School, Ann Arbor, Mich.	The Psychophysiology of the Photopupillary Mechanism	3,600
Auerbach, Edgar, M.D. (continuation)	Vision Research Laboratory, Hadassah University Hospital and Medical School, Jerusalem	Light and Color Perception; Participation and Specification of Recepter Mechanisms in Normal and Pathological Conditions	4,500
Balazs, Endre A., M.D. (continuation)	Retina Foundation, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston	Studies on the Hyaluronic Acid Formation of the Vitreous Body	4,000
Breinin, Goodwin M., M.D. (continuation)	Department of Ophthalmology, New York University Post-Graduate Medical School-Bellevue Medical Center, New York	Electromyography of the Extraocular Muscles Including Stimulation Studies and Evaluation of Drug Effects on the Action Current	2,500
Burns, Robert P., M.D. (continuation)	Department of Ophthalmology, Columbia University College of Physicians and Surgeons, New York	Tissue Culture of Cytomegalic Inclusion Disease Virus with Electron Microscope Studies	1,850
Cibis, Paul A., M.D. (continuation)	Department of Ophthalmology, Washington University School of Medicine, St. Louis	Histopathology of the Eye with Oblique Illumination	4,000
Donn, Anthony, M.D.	Department of Ophthalmology, Columbia University College of Physicians and Surgeons, New York	The Active Transfer of Sodium Across the Corneal Epithelium	1,800
Eliasson, Sven G., M.D. (continuation)	Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Texas	The Role of Visual Impulses in the Control of Eye Muscle Activity	5,000
Ellerbrock, V. J., Ph.D. (continuation)	School of Optometry, Ohio State University, Columbus, Ohio	Preparation of Textbook on Partial Sightedness	250
Fisher, Earl, Jr., Ph.D.	Department of Ophthalmology, Tulane University School of Medicine, New Orleans	Mechanism of Corneal Damage Following Certain Bacterial Infections	2,160
Garron, Levon K., M.D., and Foerster, Helenor Campbell (continuation)	Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine, San Francisco	Special Histopathologic Study of Endogenous Uveitis	4,000

Investigator	Institution	Project Title	Amount
Goldberg, Bernard, M.D., and Tabowitz, David, B.A.	Department of Research, Division of Radioisotopes, New York Eye and Ear Infirmary, New York	Development of Improved Instrumentation Using Radioisotope Techniques in the Clinical Differentiation of Malignant Melanomas from Inflammatory Lesions of the Anterior Ocular Segment	$3,000
Green, Harry, Ph.D. (continuation)	Research Department, Wills Eye Hospital, Philadelphia	Elaboration of the Bicarbonate Ion in Aqueous Humor and Its Relation to the Dynamics of Aqueous Flow	5,500
Hanna, Calvin, Ph.D.	Department of Pharmacology, University of Vermont College of Medicine, Burlington, Vt.	Studies on Cataract Formation: Nucleic Acid Changes in the Normal and Radiated Eye	3,000
Hepner, Ray, M.D. (continuation)	Department of Pediatrics, University of Missouri School of Medicine, Columbia, Mo.	The Effects of Maternal Hyperoxemia on the Intrauterine Development of the Eye	1,000
Jacobson, Jerry Hart, M.D. (continuation)	Department of Electrophysiology, New York Eye and Ear Infirmary, New York	Differential Electroretinography in Clinical Ophthalmology	1,500
Jampolsky, Arthur, M.D.	Department of Ophthalmology, Stanford University Hospital and School of Medicine, San Francisco	Study of Eye Movements by High Speed Photography	2,000
Kirber, Maria W., Ph.D.	Department of Bacteriology, Women's Medical College of Pennsylvania, Philadelphia	Experimental Viral Uveitis	2,500
Langham, Maurice E., Ph.D.	Institute of Ophthalmology, University of London	Regulation of the Intraocular Pressure	1,200
Maumenee, A. Edward, M.D.	Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore	Antigen-Antibody Reactions in the Rabbit Cornea	5,000
Michaelson, I. C., M.D. (continuation)	Department of Ophthalmology, Hadassah University Medical School, Jerusalem	The Arthus, Schwartzmann, Precipitation, and Corneal Graft Allergic Phenomena in the Cornea with Particular Reference to their Dependence on the Presence of Corneal Blood Vessels	2,000
Mitsui, Yukihiko, M.D.	Department of Ophthalmology, Kumamoto University Medical School, Honjomachi, Japan	Prevention of Epidemic Keratoconjunctivitis by Vaccination	1,200
Pirie, Antoinette, Ph.D.	Nuffield Laboratory of Ophthalmology, Oxford University	Study of Changes in the Constituents, Metabolism, and Histology of the Lens During Development of Cataract	3,000

Investigator	Institution	Project Title	Amount
Sloan, Louise L., Ph.D.	Wilmer Institute, The Johns Hopkins University School of Medicine, Baltimore	Clinical Significance of the AC/A Ratio	$2,646
Smelser, George K., Ph.D. (continuation)	Institute of Ophthalmology, Columbia University College of Physicians and Surgeons, New York	Relations of the Exophthalmogenic and Thyrotropic Pituitary Principles	900
Solanes, M. Pugi, M.D. (continuation)	Department of Ophthalmology, General Hospital, México, D. F.	Comparative Anatomical and Physiological Study of the Structures Related to to the Maintenance of Intraocular Pressure in Mexican Indians and "White People"	961
Thornfeldt, Paul R., M.D.	Good Samaritan Hospital Research Foundation, Portland, Ore.	An Investigation of the Presence of Hyaluronidase-Sensitive Mucopolysaccharide in Tissues of Filtration Angle of Fetal and Infantile Eyes	675
Wilson, Fred M., M.D.	Department of Ophthalmology, Indiana University School of Medicine, Indianapolis	Evaluation and Localization of Possible Glaucomatogenic Effects of Experimental β-Irradiations of the Limbus	1,500
Wolken, Jerome J., Ph.D. (continuation)	Biophysical Research Laboratory, Eye and Ear Hospital, University of Pittsburgh School of Medicine, Pittsburgh	Photoreceptor Structures	2,500
Zimmerman, Lorenz E., M.D.	Episcopal Eye, Ear and Throat Hospital, and Armed Forces Institute of Pathology, Washington, D. C.	Pathology, Pathogenesis, Prevention, and Treatment of Fungus Infections of the Eye	5,150

Special Grants

11-Cisisomer of vitamin A in the prevention of retinal rod degeneration: $500 to aid in the preparation and presentation of a paper on this study which was initiated in 1955 under a Fight For Sight Research Fellowship to Albert B. Chatzinoff, M.D., at The Mount Sinai Hospital, New York.

Trachoma mobile unit: $7,500 to aid the Department of Ophthalmology of the Hadassah University Medical School, Jerusalem, in extending its trachoma control program through examination and treatment to the populations in outlying sections where such medical care is inaccessable. This unit, under the direction of I. C. Michaelson, M.D., is being created with the view that it will serve as a model for the establishment of other such units in that area of the world.

International Symposium on Photoreception: $850 to underwrite a portion of the cost of organizing and conducting a Symposium on Photoreception held on Jan. 31 and Feb. 1, 1958, under the auspices of the New York Academy of Sciences, Biology Section. Jerome J. Wolken, Ph.D., of the Biophysical Research Laboratory, Eye and Ear Hospital, University of Pittsburgh, who has been engaged in the study of photoreceptor structures of the eye with the aid of Fight For Sight Awards, served as general chairman of the Symposium.

Studies in amblyopia and glaucoma: $672 to Walter Kornblueth, M.D., Hadassah University Medical School for travel costs to enable the investigator to spend one year at the Sanford University School of Medicine, Department of Ophthalmology, in full-time research with Arthur Jampolsky, M.D., Milton Flocks, M.D., and Earl McBain, M.D.

Full-Time Research Fellowships

Fellow	Direct Supervisor	Institution	Project Title	Amount
Barishak, Robert Y., M.D. (continuation)	Michael J. Hogan, M.D.	Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine	Tissue Culture of Malignant Melanomas	$3,600
Brandt, Philip W., M.S.	George D. Pappas, Ph.D., and George K. Smelser, Ph.D.	Departments of Anatomy and Ophthalmological Research, Columbia University College of Physicians and Surgeons	Study of the Cytological Mechanism of Fluid Transport Through the Membranes in the Anterior Segment of the Eye by Methods of Light and Electron Microscopy	3,400
Holmberg, Ake Siguard, M.D.	Bernard Becker, M.D.	Departments of Ophthalmology and Anatomy, Washington University School of Medicine	Ultrastructure of the Cilary Epithelium and Its Connection with Secretion of Aqueous Humor	5,000
Krishna, Narendra, M.D. (continuation)	Irving H. Leopold, M.D.	Department of Ophthalmology, University of Pennsylvania School of Medicine	Electromyography and Related Electrophysiologic Techniques in Ophthalmology	4,000
Tokunaga, Tsugihiko, M.D.	P. J. Leinfelder, M.D.	Department of Ophthalmology, University Hospitals, State University of Iowa	I. Cytological Study by Electron Microscopy on Radiation Cataract II. Study on Incipient Opacities of Experimental Cataracts	4,800
Wania, Jamshed, H., M.D.	Frank Walsh, M.D.	Wilmer Institute, The Johns Hopkins University School of Medicine	Studies in Neuro-Ophthalmology (tenure—3½ months)	700
Waton, Nicholas G., Ph.D.	F. W. Schueler, Ph.D.	Department of Pharmacology, Tulane University School of Medicine	The Nature of Central and Peripheral Synaptic Transmission in the Optic Pathway	5,000

Summer Student Fellowships

Fellow	Direct Supervisor	Institution	Project Title	Amount
Barasch, Kenneth Robert	John McLean, M.D., and Miles Galin, M.D.	Department of Ophthalmology, New York Hospital, Cornell Medical Center	Effects of Blood Plasma Volume and Osmolacity on Intraocular Pressure	$600
Crawford, William F.	Michael J. Hogan, M.D.	Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine	Research on Mast Cells, Including Differential Stains and Sequential Gross Studies	600
Ernest, J. Terry	Frank W. Newell, M.D.	Section of Ophthalmology Department of Surgery, University of Chicago	Dynamics of Water Transport in the Eye	600
Giles, Kenneth M.	John E. Harris, Ph.D., M.D.	Department of Ophthalmology, Weeks Memorial Laboratory, University of Oregon Medical School	Transport of Glucose Across the Lens Surface	600
Henkind, Paul	George N. Wise, M.D.	Department of Ophthalmology, New York University-Bellevue Medical Center	Study of Descemet's Folds in Diabetic and Normal Human Subjects	600
Innes, James Walker	John McLean, M.D., and Miles Galin, M.D.	Department of Ophthalmology, New York Hospital-Cornell Medical Center	Study on the Physiology of Corneal Elasticity as Related to Certain Ocular Disease States	600
Katz, Joseph	Peter H. Ballen, M.D.	Department of Ophthalmology, Kings County Hospital-Downstate Medical Center, State University of New York	Use of Acrylics of the Nonpolymerizing Type in Restoration of the Enucleated and Eviscerated Socket	600
Madison, James B.	F. W. Schueler, Ph.D.	Department of Pharmacology, Tulane University School of Medicine	Determination of the Effects of Hemicholinium upon Intraocular Pressure	600
Muskat, David	Jerome J. Wolken, Ph.D.	Biophysical Research Laboratory, Eye and Ear Hospital, University of Pittsburgh Medical Center	Problems in Photoreception Related to the Problems of Vision, Energy Transfer, and Photosynthesis	400

Fellow	Direct Supervisor	Institution	Project Title	Amount
O'Brien, James Edward	Calvin Hanna, Ph.D.	Department of Pharmacology, University of Vermont College of Medicine	Intracellular Biochemical Changes in the γ-Ray-Treated Eye	$600
Rubin, Laurence Edward	Marguerite Constant, Ph.D.	Department of Ophthalmology, Washington University School of Medicine	Diabetic Retinopathy	600
Sabey, Andrew Charles	James L. McGraw, M.D.	Department of Ophthalmology, Upstate Medical Center, State University of New York	I. Experimental and Clinical Study of Postoperative Wound Hemorrhage in Ophthalmic Surgery II. Effects of Iproniazid (Marsilad) and Related Amine Oxidase, Inhibitors on Intraocular Pressure	$600
Shepherd, Gordon Murray	J. Downer, Ph.D.	Department of Physiology, Harvard Medical School	A Study of the Influence of Visual Cortex on the Cortical Control of Movement	600
Srebro, Richard	Bernard Becker, M.D.	Department of Ophthalmology, Washington University School of Medicine	A Stress-Strain Curve for Sclera	600
Starr, Wilson Clayton	Banks Anderson, M.D.	Division of Ophthalmology, Department of Surgery, The Duke University School of Medicine	Evaluation of Results of Surgery in Glaucoma	600
Stiles, James Fleming	Ralph G. Jane, Ph.D.	Department of Anatomy, State University of Iowa College of Medicine	Distribution in the Rabbit Eye of C^{14}-Labelled Compounds	600
Stobbe, Juergen A.	Arthur H. Keeney, M.D.	Section on Ophthalmology, University of Louisville School of Medicine	Action of Lyophilized Vitreous on Experimentally Produced Hematogenous Opacities in the Rabbit Vitreous	600

Fellow	Direct Supervisor	Institution	Project Title	Amount
Traugh, George Holton, Jr.	Wolfgang A. Lieb, M.D.	Department of Ophthalmology, Medical College of Virginia	Clinical and Experimental Study on the Incidence of Eye Disorders in Sickle-Cell Anemia and Hemoglobin-C Disease	$600
Tsang, Wallace	Michael J. Hogan, M.D.	Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine	Study of Development of Angle of Anterior Chamber in Embryo and Fetal Eyes with Use of Carbohydrate and Trichrome Stains	600
Varriale, Philip	Abraham Schlossman, M.D.	Department of Ophthalmology, Kings County Hospital-Downstate Medical Center, State University of New York	Pleoptics in Management of Strabismus	600
Young, Robert Rice	S. W. Kuffler, Ph.D.	Neurophysiology Program, Marine Biological Laboratory	A Study of the Energetics of Generator Potentials	500

VI Pan American Congress of Ophthalmology.—The VI Pan American Congress of Ophthalmology will convene in Caracas, Venezuela, from Jan. 31 to Feb. 7, 1960.

The scientific program includes symposia on Virus Diseases in Ophthalmology, Toxoplasmosis, Genetics, Strabismus, Detachment of the Retina, Medical Advances in Ophthalmology, Surgical Advances in Ophthalmology, Therapy of Infectious Diseases, Surgery of Strabismus, Surgery of Cataract, and Space Ophthalmology.

Free papers will be accepted and should be submitted to the Chairman of the Program Committee, Dr. James H. Allen, 1430 Tulane Ave., New Orleans, up to June 1, 1959.

Movies will also be accepted provided that they have not been shown previously and that the author will be present at the meeting to answer any questions regarding the movie.

There will be a scientific exhibition. Details about this exhibition can be obtained from Dr. James H. Allen.

The Congress has the full backing of the government of Venezuela, and the government of that country especially wants to welcome all ophthalmologists from the Americas.

Caracas is a very beautiful city, with an altitude of 2,700 feet, which makes its climate very temperate, especially in January and February.

It has very good hotels and is linked by a super highway with the port of La Guaira, where the airport for Caracas is also located. The trip from La Guaira to Caracas takes only 20 minutes.

It has been decided that reservations should be made directly to Mr. Gus A. Romea, Hotel Tamanaco, Caracas, Venezuela, who will assign the rooms to those who request them, according to the dates of the requests. The Tamanaco Hotel will be the headquarters of the Congress. The scientific meetings will be held at the University, where there is a very large auditorium equipped with earphones, thus facilitating simultaneous translation.

Prices in Caracas are no higher than they are in the United States, and there is a very large number of United States citizens living in Venezuela, around 25,000.

The Local Committee has planned a very interesting social program, so that the VI Pan American Congress of Ophthalmology will be at least as good as the others which preceded it.

Please write to Dr. Moacyr E. Alvaro, Executive Director of the Pan American Association of Ophthalmology, 1151 Consolação, São Paulo, Brazil, for any further information regarding the meeting. One may also write to Dr. J. Wesley McKinney, Secretary for north of Panama, Suite 921, Exchange Building, Memphis, and to Dr. William L. Benedict, Chairman of the Committee on Congresses, 15 2d St. S. W., Rochester, Minn.

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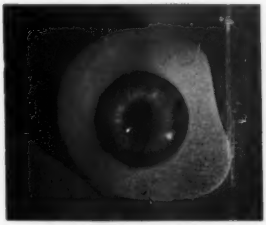

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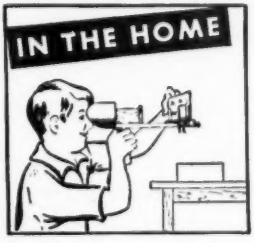

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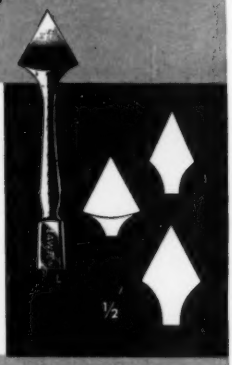

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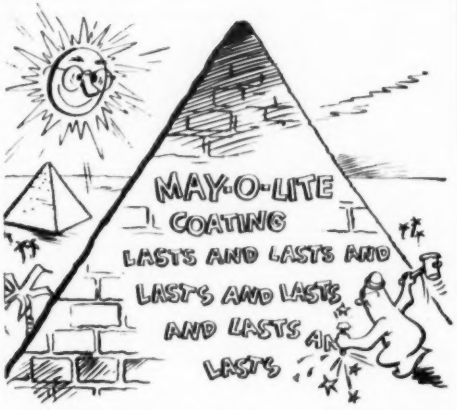

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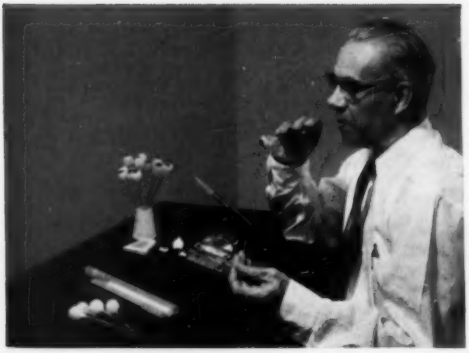

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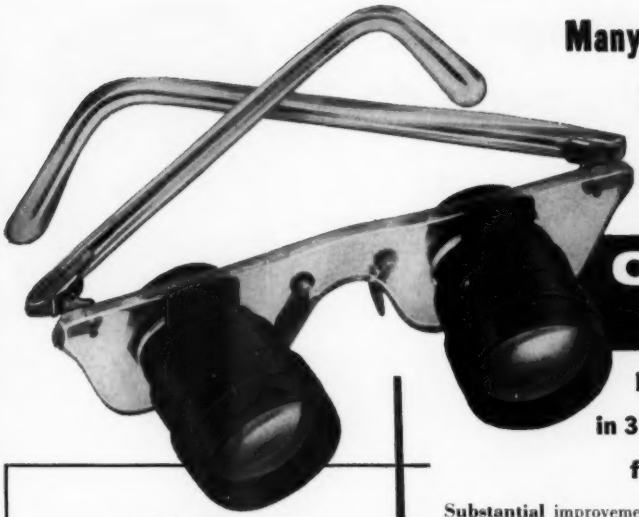

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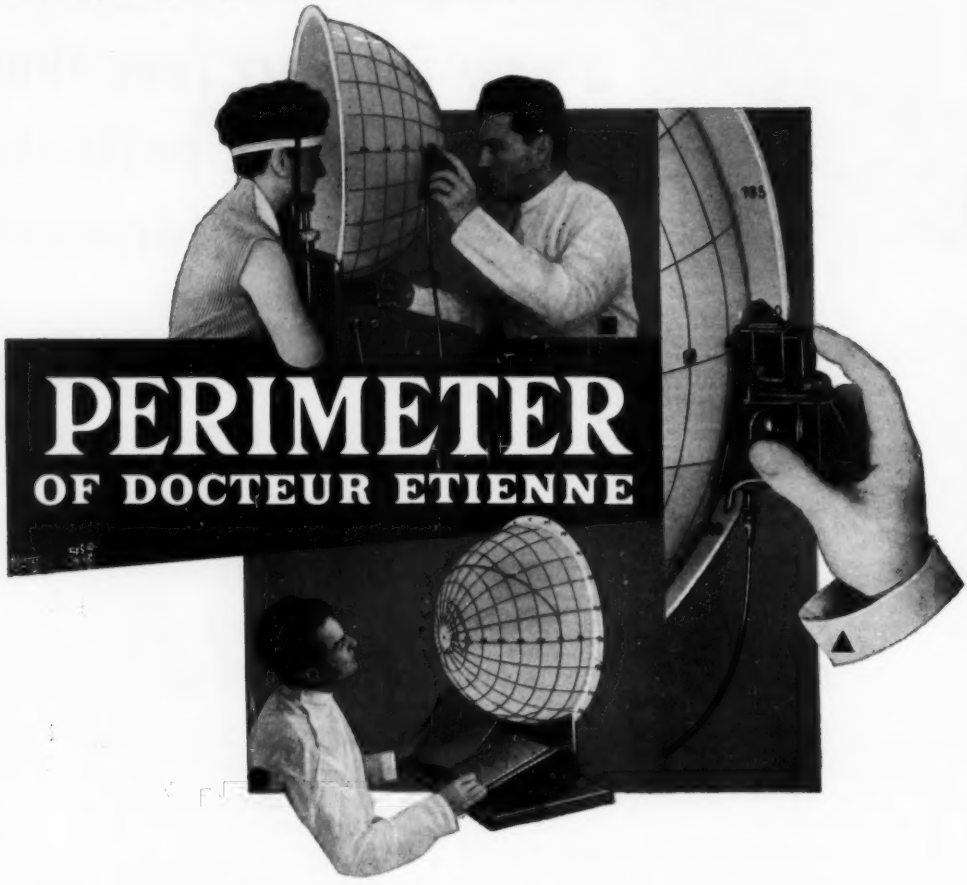

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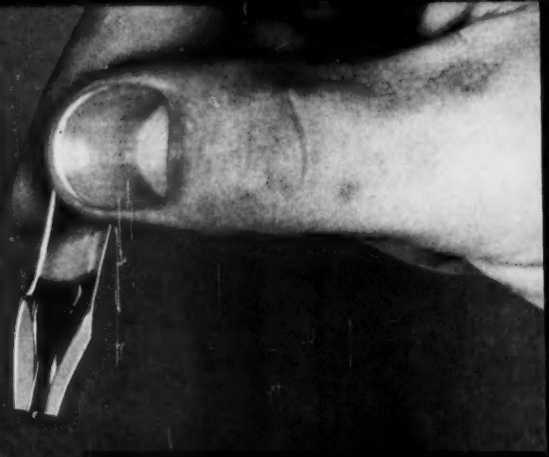

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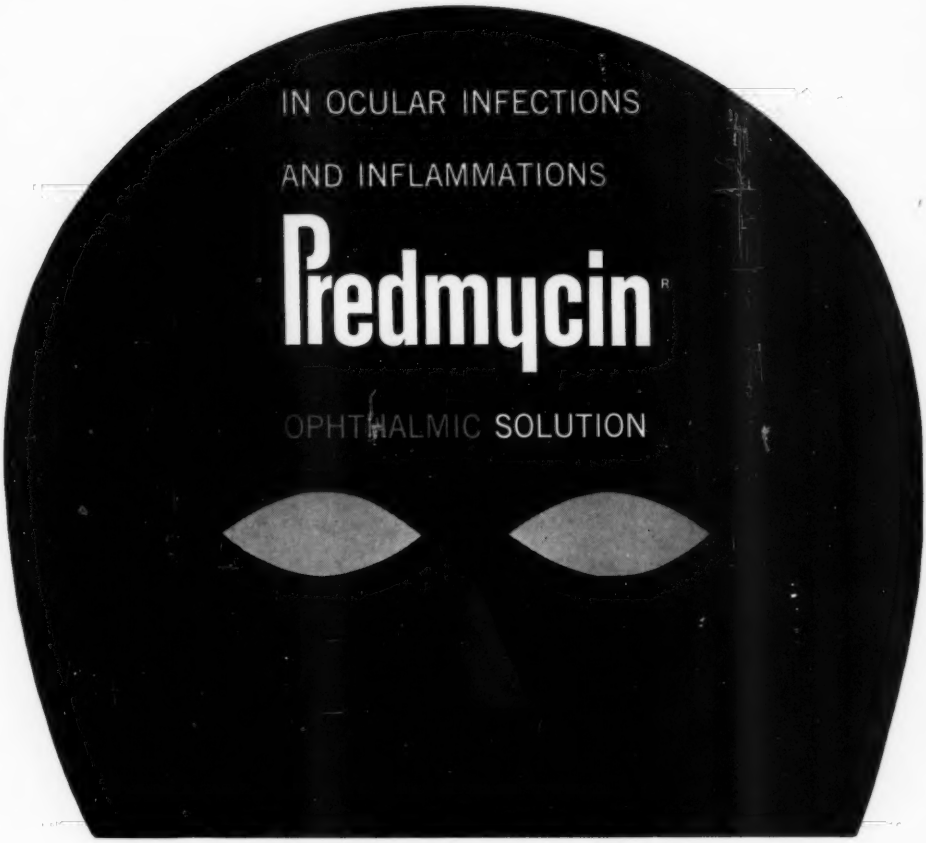

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